

The Right Ventricle in Adult Congenital Heart Disease

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Statement of Original Authorship

The material in this Thesis has not previously been submitted for a degree in any University. It contains, to the best of my knowledge, no material written or published by another person except where due acknowledgement is made in the Thesis itself.

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Para ti – te quiero. Siempre.

“All men dream; but not equally. Those who dream by night in the dusty recesses of their minds wake in the day to find it was vanity. But the dreamers of the day are dangerous men, for they may act their dreams with open eyes, to make it possible”.

T E Lawrence

ABSTRACT

Heart failure (HF) and sudden cardiac death (SCD) in congenital heart disease (CHD) is prevalent and can relate to abnormal right ventricular (RV) physiology and abnormalities of QRS duration, and QRS, JT and QT dispersion (d). Characterising disease and identifying factors that may predict adverse outcome in those with either a subpulmonary or subsystemic RV, as well as investigating potential avenues to ameliorate abnormal RV physiology is necessary to improve outcomes in this young population.

I undertook several studies during the course of this Thesis to examine and further understand these two separate physiological substrates: In the first I studied the effect of isolated percutaneous (PPVI) pulmonary valve implantation on surface ECG parameters. PPVI represents a pure model of RV mechanical and electrophysiological changes post replacement as compared to surgical replacement: Ninety nine PPVI procedures in patients with CHD (aged 23.1 ± 10 yrs) were studied pre, post and 1-year following PPVI with serial ECG's and echocardiography/ magnetic resonance imaging (CMR). 43% had pulmonary stenosis, 27% pulmonary regurgitation (PR) and 29% mixed lesions. In those with predominantly PR (n=26), QRS duration decreased significantly (135 ± 27 to 128 ± 29 ms; $p=0.007$). However, in the total cohort no significant change in QRS duration at 1 year was observed (137 ± 29 to 134 ± 29 ms). QTc, QRSd, QTd and JTd all significantly reduced at 1 yr ($p \leq 0.001$). RV EDV correlated with pre-procedure QRS duration ($r=0.34$; $p<0.002$) but there was no correlation after PPVI. This is the first study to report electrical remodelling following isolated PPVI and it confirms that reductions in QRS duration occur post PPVI in PR, as reported for equivalent surgical cohorts. Further, increased homogeneity of repolarisation, in combination with improved conduction, may reduce arrhythmic events in congenital cardiac patients with pulmonary valvular disease.

My second study sought to create an epicardial electroanatomic map of the RV and then apply post-operative targeted single and dual site RV temporary pacing with measurement of haemodynamic parameters. I wished to determine the potential role of cardiac resynchronization therapy (CRT) in the setting of RV dysfunction as little is known regarding the potential benefits of CRT in this setting. Sixteen adults (age= 32 ± 8 yrs, 6M; 10F) with right bundle branch block (RBBB) and repaired tetralogy of Fallot (ToF; n=8) or corrected congenital pulmonary stenosis (n=8) undergoing surgical pulmonary valve replacement (PVR) for PR underwent intra-operative epicardial RV mapping and haemodynamic assessment of random pacing configurations including site of latest RV activation.

I found that the commonest site of latest activation was the RV free wall & dual chamber (DDD) pacing here, alone or combined with RV apical pacing, resulted in significant increases in cardiac output (CO) vs AAI pacing ($p<0.01$ all measures). DDD RV alternative site pacing significantly improved CO by 16 % vs AAI, and 8.5% versus DDD RV apical pacing ($p=0.02$). Single site RV pacing targeted to the region of latest activation in patients with RBBB undergoing PVR thus induces acute improvements in haemodynamics and implies that targeted pacing in such patients has therapeutic potential both post-operatively and in the long term.

QRS duration is a strong predictor of survival in acquired left ventricular dysfunction, but equivalent data in those with a systemic RV is lacking. My next studies investigated not only the relationship between ECG parameters, arrhythmia burden and outcome in adults with transposition of the great arteries (TGA) late after atrial switch repair, but also the interrelationships between various HF markers in this cohort. Adults with Senning or Mustard palliation of TGA under follow up at a dedicated congenital HF clinic and 13 similar adults who suffered a cardiac death were included for study. Patients were subdivided by arrhythmic history, surgical intervention and death. Assessment included symptom assessment, venous blood sampling for circulating N-terminal pro brain natriuretic peptide (NT-proBNP) levels, measurement of surface ECG and CMR for the assessment of RV systolic function and determination of indexed RV volumes.

I found that QRS duration ($p=0.0003$) and QTc interval ($p=0.0009$) increase significantly with changing arrhythmia subtype, and that both QRS and QTc were independently associated with increased risk of death: for 1ms increase in QRS HR 15 [95% CI 3.3-68.6] and for QTc HR 10.7 [95% CI 2.3-49] ($p<0.0001$ for both). QRS >104 ms and QTc >406 ms had a sensitivity/specificity for predicting death of 96%/66% and 96%/56% respectively. Two year mortality was 36% when QRS <104 ms and 88% when >104 ms ($p<0.0001$ for difference). Further, compared to those with uncomplicated surgery, patients with complex surgical history had higher NT-proBNP levels (55 ± 26 vs 20 ± 35 pmol/L; $P=0.002$) and longer QRS duration (116 ± 28 ms vs 89 ± 11 ms; $P=0.0004$) whilst showing no difference in NYHA class and RV function. There was a significant relationship between diastolic and systolic RV volumes and both NT-proBNP levels ($r=0.43$, $P=0.01$; $r=0.53$, $P=0.001$ respectively) and QRS duration ($r=0.47$, $P=0.004$; $r=0.53$, $P=0.001$ respectively).

These findings suggest that QRS width and corrected QTc interval on surface ECG are associated with increased risk of death in adults late after atrial switch repair of TGA. Given that a QRS of only 104ms defines a high risk population, careful examination of the ECG is desirable in all patients and therapy to reduce risk attempted. Further, together with these simple surface ECG parameters, circulating NT-proBNP levels constitute safe, cost effective and widely available surrogate markers of

systemic RV function and provide additional information on heart failure status. Both measures hold promise as prognostic markers and their association with long-term outcome should be determined.

Lastly, I examined the mechanisms of late RV failure and studied their relationship to subjective quality of life assessment as this are poorly characterised. Equilibrium Contrast CMR imaging was used to quantify extracellular volume (ECV) in the septum and RV free wall of adults presenting to a specialist clinic late after atrial redirection surgery for TGA. These were compared to age and sex matched healthy volunteers. Patients were also assessed with a standardised CMR protocol, NT-proBNP and surface ECG measurement, and cardiopulmonary exercise (CPEX) testing. Patients also completed a Minnesota Living With Heart Failure Questionnaire (MLHFQ) self assessment.

I determined that mean septal ECV was significantly higher in patients than controls (0.254 ± 0.036 , vs 0.230 ± 0.032 ; $p=0.03$). NT-proBNP positively related to septal ECV ($p=0.04$; $r=0.55$) but chronotropic index (CI) during CPEX testing negatively related to ECV ($p=0.04$; $r=-0.58$). No relationship was seen with other CMR or CPEX parameters. Median MLHFQ score was 6(2-19), median NT-pro BNP 24 (16-43) and mean peak VO_2 24 ± 7 mL/kg/min. There was a significant positive correlation between MLHFQ score and NT-proBNP ($p=0.001$, $r=0.34$) and a significant negative correlation with peak VO_2 ($p=0.001$, $r=0.49$).).

Septal interstitial expansion is seen in adults late after atrial redirection surgery for TGA. It correlates well with NT-proBNP and CI and may have a role in the development of RV systolic impairment. The MLHFQ correlates highly with NT-proBNP and exercise capacity in patients with systemic RV impairment. The ability of the MLHFQ in predicting HF events and prognosis in adults with CHD needs further evaluation.

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ABBREVIATIONS AND DEFINITIONS

AAI	-	Atrial Demand Inhibited Pacing
APD	-	Action potential duration
AV	-	Atrioventricular (delay; ms)
CHD	-	Congenital heart disease
CI	-	Cardiac Index (L/m^2)
ChI	-	Chronotropic Incompetence
CMR	-	Cardiac magnetic resonance
CO	-	Cardiac Output (L/min)
CRT	-	Cardiac resynchronisation therapy
CPEX	-	Cardiopulmonary exercise testing
DDD	-	Dual chamber pacemaker device
ECG	-	Electrocardiography
ECV	-	Extracellular volume
EDV(i)	-	End diastolic volume (indexed – ml/m^2)
EF	-	Ejection fraction (%)
EGM	-	Electrogram
ESV(i)	-	End systolic volume (indexed – ml/m^2)
HF	-	Heart failure
ICD	-	Implantable cardioverter defibrillator
LBBS	-	Left bundle branch block
LGE	-	Late Gadolinium enhancement
LV	-	Left ventricle
MAP	-	Mean arterial pressure

MLWHFQ	-	Minnesota living with heart failure questionnaire
NT-proBNP	-	Brain Natriuretic Peptide (pmol/L)
NYHA	-	New York Heart Association (functional class)
PPVI	-	Percutaneous pulmonary valve implantation
PR	-	Pulmonary regurgitation
PS	-	Pulmonary stenosis
PVR	-	Pulmonary valve replacement (surgical)
RBBB	-	Right bundle branch block
RV	-	Right ventricle
RVOT	-	Right ventricular outflow tract
SCD	-	Sudden cardiac death
SV	-	Stroke volume (ml/min)
SVT	-	Supraventricular tachycardia
TGA	-	Transposition of the Great Arteries
ToF	-	Tetralogy of Fallot
UE	-	Urea & electrolytes
VE/VCO ₂	-	Minute ventilation-carbon dioxide production relationship
VO ₂	-	Oxygen uptake (on exercise)
VT	-	Ventricular tachycardia

QRS duration, QTc and QT/QRS/JT dispersion: measurable components of the surface ECG (ms).

INTRODUCTION

1. Congenital Heart Disease

1.1 Definition and Incidence

Congenital heart disease (CHD) can be defined as any malformation of the heart or intrathoracic great vessels that is present from birth. It encompasses a wide range of anatomic variety, from the intuitively minor patent foramen ovale to the gross malformations of cardiac structure as might occur in hypoplastic left heart syndrome.

Recent advances in surgical and catheter interventions have ensured that those born with haemodynamically significant lesions are surviving longer, and as a consequence, the end of this last decade saw the same number of adults as children alive with complex CHD for the first time¹. Given that the incidence of all forms of CHD is placed at between 4 to 19 per 1000 live births^{1,2}, there are an estimated 2-4 million patients alive in Europe of whom 1.2-2.7 million are aged greater than 15 years³.

The significance of the size of this population is made starkly clear when one considers the average age of death of the total cohort: 37±15 years. Leading causes of death comprise heart failure (HF) and sudden cardiac death (SCD)^{4,5}. Despite such remarkable progress therefore over the past few decades, these patients retain a high burden of morbidity and mortality compared to their healthy peers. There is a paucity of evidence based medicine to identify patients at risk of adverse events and a further lack of empirical outcome assessed research. Such lack of data is in part, due to the wide variety of anatomic lesions comprising the total cohort – comparison within haemodynamic subtypes has often entailed few numbers, certainly not on the scale that has driven research in those with acquired or cardiomyopathic heart disease.

There is, in the young and burgeoning high risk population with CHD, a pressing need to understand the pathophysiological mechanisms underlying the different anatomic substrates and to develop effective therapeutic strategies. To that end, this Thesis will study two different models of right ventricular pathophysiology occurring in CHD – the subpulmonary right ventricle such as in repaired tetralogy of Fallot, and the systemic right ventricle as it occurs in palliated transposition of the great arteries.

1.2 The Right Ventricle

The RV is the most anterior cardiac structure, lying immediately posterior to the sternum. Its anatomic boundaries are the tricuspid valve and the pulmonary valve, and it is comprised of three distinct regions: the *inlet* includes the tricuspid valve with its chordate tendinae and papillary muscles, the *apical* portion is heavily trabeculated and contains the chamber-defining moderator band, and lastly the *infundibulum* which forms the continuous smooth, muscular outflow tract⁶.

The primary function of the normal RV is to pump blood from the systemic venous circulation to the lungs via the pulmonary arteries. It forms a circuit with the LV and maintains a similar stroke volume; however, the RV is a thin-walled structure encompassing a low-pressure environment. Its geometry is complex and visualisation by traditional imaging methods challenging.

In CHD, the RV is often subpulmonary, but it can also occur in the subaortic position (serving the systemic circulation) or be a solitary ventricle maintaining both circulations. Disease in CHD more commonly involves the RV irrespective of its anatomic location, and can occur as a result of a number of underlying processes, including dilatation through volume loading, such as occurs in repaired ToF, or the pressure loading more often associated with the systemic or solitary type. In either situation, the underlying pathophysiology leading to HF or SCD is necessarily different than that which affects the morphologic and systemic LV. Certainly, in the population without CHD the commonest cause of RV dysfunction is secondary to left sided disease. Further, the mechanism, timing and severity of injury and potential adaptability of the RV to stress leads to differing responses in terms of neurohormonal activation, ventricular myocardial remodelling and underlying gene expression, myocardial ischaemia resulting from the original insult and/or subsequent compromise and importantly, the impact on local and ventricular electromechanical interactions. This infers that pathophysiological changes occurring in the RV cannot be directly transferred from the general population, and neither can the process be applied to all substrates of CHD. Currently however, prognostication, investigation and treatment of RV disease are applied from evidence gathered in those with LV disease; the transfer value to RV pathophysiology in CHD has not been formally assessed.

1.2.1 The Subpulmonary Right Ventricle

The model I have chosen for this anatomy is repaired tetralogy of Fallot (ToF). ToF is the commonest cyanotic congenital heart defect with an estimated incidence of 0.3 per 1000 live births⁷. The

average age at death in this cohort is 41 ± 15 years, with SCD (31%), HF (25%) and perioperative mortality (8%) constituting the commonest modes of death⁴.

The four features typical of ToF include an overriding aorta, unrestrictive ventricular septal defect, right ventricular outflow tract obstruction (infundibular stenosis) and a compensatory right ventricular hypertrophy (Figure 1).

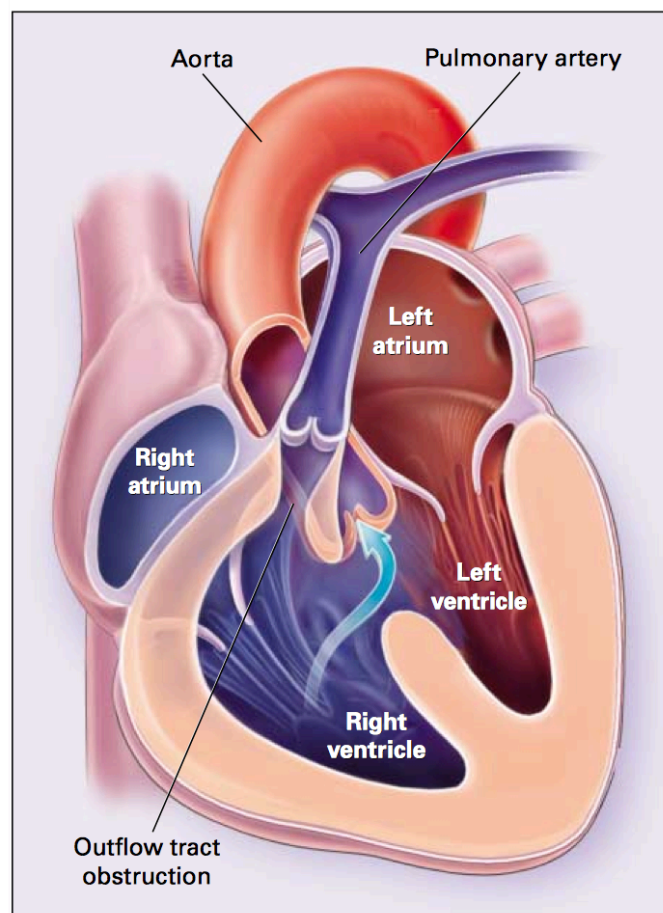


Figure 1: Anatomic representation of the typical features of tetralogy of Fallot: Ventricular septal defect, overriding aorta, RV hypertrophy and RV outflow tract obstruction (pulmonary stenosis). From Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. N Engl J Med. 2000 Feb 3;342(5):334-42 Copyright © (2014) Massachusetts Medical Society. Reprinted with permission.

The underlying pathology arises as a consequence of underdevelopment of the RV infundibulum causing malalignment of the infundibular septum. Males and females are affected equally, and the incidence is sporadic.

Infants diagnosed with ToF nowadays undergo successful repair between the ages of 3-6 months⁸. The techniques used to correct the underlying anatomy have evolved considerably since first attempted in the 1950's: Extensive right ventriculotomy and trans-annular intervention is avoided where possible now in favour of less invasive approaches. It is not uncommon however, to encounter a young adult at follow-up with progressive RV dilatation, RV dysfunction and significant pulmonary valve regurgitation. Due to such residual lesions following primary repair, patients often require further surgery in their 20's and 30's to implant a competent pulmonary valve. The haemodynamic impact of early surgery and progressive pulmonary valvular insufficiency in this cohort leads to a primarily volume overloaded pathophysiology of the RV.

1.2.2 The Systemic Right Ventricle

There is an anatomic subtype of CHD where the normal ventriculo-arterial relationship is inverted. Complete transposition of the great arteries (TGA) is the commonest cause of neonatal cyanosis with an incidence of 2-3 per 10,000 live births⁹. In this anatomy there is atrio-ventricular concordance with ventriculo-arterial discordance such that a parallel circulation is in effect, allowing no mixing of pulmonary and systemic blood unless a concomitant defect also exists, most commonly a septal defect at atrial or ventricular level (Figure 2). Palliation is achieved via atrial switch redirection surgery (Mustard or Senning procedure), which was routinely undertaken prior to the advent of the arterial switch, or Jatene, procedure in the mid-1980's. Co-existing ventricular septal defects are closed at the time of surgery; however they enable further differentiation of anatomy into *simple* – intact ventricular septum, and *complex* – with ventricular septal defect.

The atrial switch operations restore a physiologic 'in series' circulation by redirecting venous return at atrial level via the creation of pathways, or 'baffles', however they commit the morphologic RV to the subaortic position and lifelong maintenance of the systemic circulation (Figure 3). The Mustard procedure uses autologous or synthetic material to create the intra-atrial baffle¹⁰, whereas the Senning procedure utilises native right atrial or intra-atrial wall tissue¹¹.

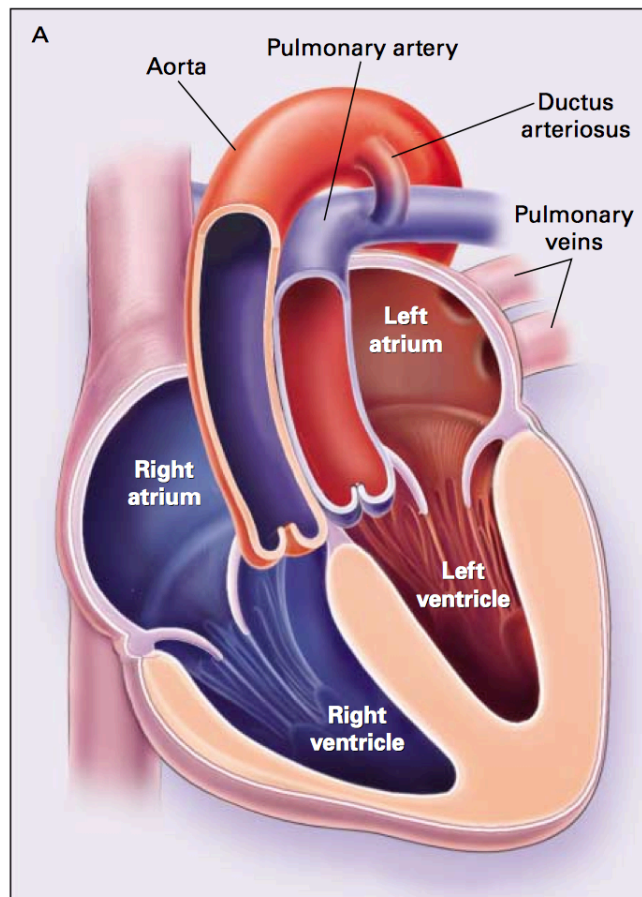


Figure 2: Complete transposition of the great arteries with intact ventricular septum. The systemic venous return to the heart enters the right ventricle and subsequently returns to the body via the aorta. Meanwhile, the morphologic LV pumps pulmonary venous return back into the pulmonary circulation. Without a concomitant atrial, ventricular or ductal defect, infants with this anatomy cannot survive. From Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. N Engl J Med. 2000 Feb 3;342(5):334-42 Copyright © (2014) Massachusetts Medical Society. Reprinted with permission.

The later developed Jatene procedure¹² switches both the aorta and pulmonary artery at root level such that the normal ventriculo-arterial anatomic relationships are re-established and preserved. Providing that anatomy is favourable, the so-called arterial switch operation is the procedure of choice; patients are only now starting to enter long-term care as adults. This Thesis will only concern itself with the atrial switch procedures and the resultant systemic RV physiology.

In this cohort of patients, the life-long maintenance of the systemic circulation by the morphologic RV leads to a pressure loaded pathophysiological system. The consequences of such a burden on this chamber are reflected in the poor long term outcomes of those with TGA palliated by either Mustard or Senning procedure: Gelatt *et al* found a survival rate of 89% at 5 years and 76% at 20

years of age¹³. Oechslin and colleagues established a mean age of death of 27±7 years in this cohort⁴. HF and SCD again constitute the commonest modes of death^{4,14,15} and outcome is related to the function of the systemic RV, known to deteriorate progressively with time from palliative surgery^{16,17}.

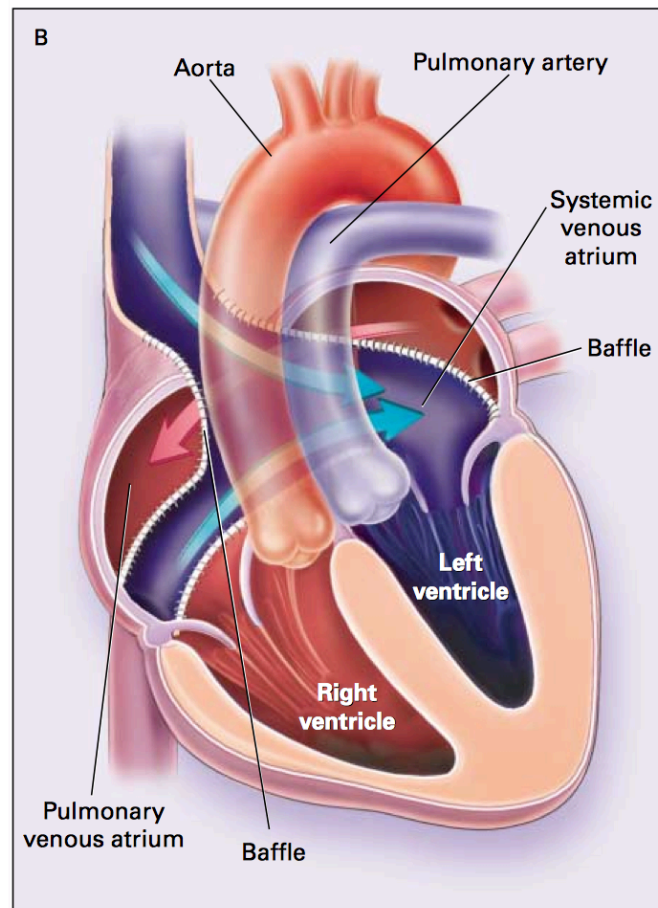


Figure 3: TGA with atrial redirection surgery. Systemic venous return to the right atrium is baffled to the morphologic LV where it is circulated to the lungs. Pulmonary venous return enters the left atrium to be redirected to the morphologic, and now systemic, RV. From Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. N Engl J Med. 2000 Feb 3;342(5):334-42 Copyright © (2014) Massachusetts Medical Society. Reprinted with permission.

1.2.3 Ventricular Interdependence

Although this Thesis concerns itself with the RV, it is neither possible nor correct to examine this chamber in isolation. Ventricular interdependence refers to the concept that the function and size of one ventricle invariably and immediately affects the other, such that the impact of disease of one ventricle is never isolated to that chamber. Ventricular interdependence can be diastolic and systolic in nature and is mediated most commonly by the interventricular septum and/or pericardium (Figure 4). This phenomenon was first alluded to by Dexter in the 1950's who described

a possible 'reverse of Bernheim's syndrome' in patients with atrial septal defect and compression of the LV by the interventricular septum¹⁸. In such patients with RV volume overload associated with atrial septal defects, device closure of the defect was found to affect an immediate improvement in LV physiology¹⁹. Therefore the presence of RV disease on the LV and possible beneficial impact on this chamber following therapy will also be discussed.

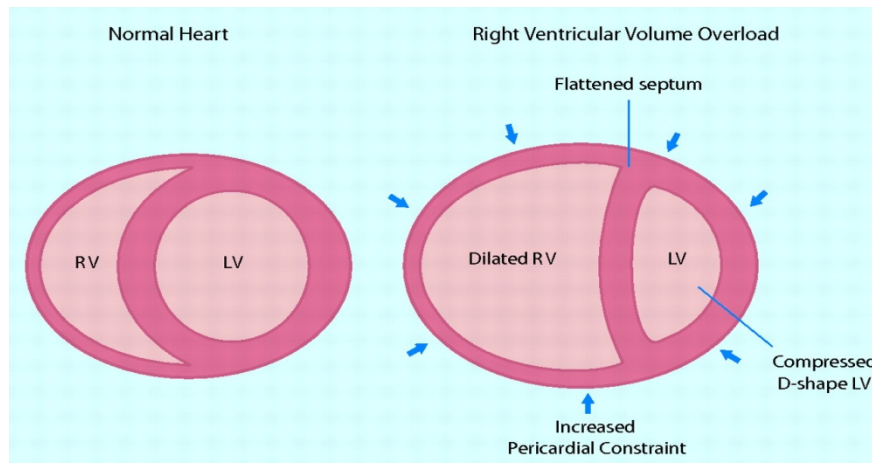


Figure 4: Ventricular interdependence in RV failure. Normal geometry is shown on the left, however with RV dilatation, as seen with volume overload, the interventricular septum is shifted toward the LV, changing the geometry of this chamber. Pericardial constraint may also occur (arrows). These changes may contribute to abnormal LV physiology in the absence of disease directly affecting this chamber. Image courtesy of Haddad F et al. *Circulation* 2008;117:1717-1731

2. Electromechanics and myocardial conduction

2.1 Normal myocardial conduction

In health, ventricular activation is propagated via the right and left bundle branches to the Purkinje network before spreading to the right and left ventricles from endocardium to epicardium. RV activation precedes LV activation, the earliest epicardial RV breakthrough site occurring at the anterior paraseptal region with subsequent radial spread towards the apex and base^{20,21,22} (Figure 5).

Descriptions of normal LV activation sequence are less consistent. Early breakthrough at the anterior paraseptal region close to the atrio-ventricular (AV) sulcus or midway between apex and base, and at a posterior paraseptal area have been described²⁰. Others report earliest breakthrough at the anterolateral region²¹, near the apex inferiorly and laterally²² with progression towards the posterolateral base²³.

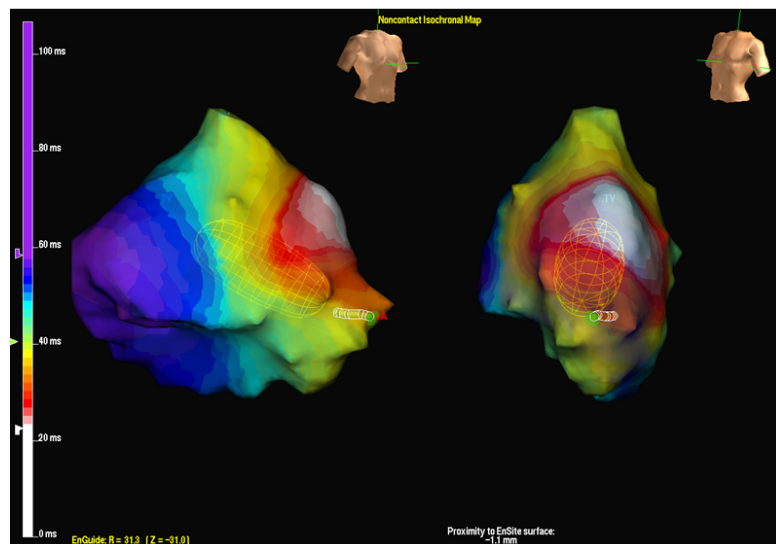


Figure 5: Isochronal activation map of the right ventricle in the structurally normal heart showing electrical activity spreading radially towards apex and base from the site of earliest breakthrough, at the anterior paraseptal region.

2.2 Abnormal myocardial conduction and bundle branch block

Electromechanics defines the interaction between the electrical activation sequence of the heart and the local mechanical response to this sequence. Delay of electrical propagation through the myocardium manifests as prolongation of the QRS duration on the surface electrocardiogram (ECG), classically described in terms of a left bundle branch block (LBBB) or right bundle branch block (RBBB) pattern. Delay in electrical propagation results in delayed regional myocardial contraction, causing *mechanical dyssynchrony* between ventricles (interventricular dyssynchrony) or within a ventricular chamber (intraventricular dyssynchrony), a phenomenon now readily quantified echocardiographically or using magnetic resonance imaging^{24,25}. Such intraventricular and interventricular dyssynchrony results in a disparity in regional and global myocardial cellular stress and strain²⁶, leading to an inefficiency of local energy production and consumption. This in turn increases the demand for myocardial oxygen, a supply which is often already compromised in those with bundle branch block.

2.2.1 Acquired Heart Disease

Canine models have shown that in the presence of LBBB (Figure 6), activation of the LV occurs by right to left trans-septal activation, followed by activation of the rest of the LV²⁷. Auricchio and colleagues refined these findings, noting that the activation wave front is unable to reach the LV lateral wall via the anterior wall due to a variable line of functional block (area of myocardium that transiently fails to propagate depolarisation wavefronts due to rate dependent changes in

refractoriness), oriented from base to apex, i.e., promoting a U-shaped activation sequence in the LV via the apex²⁸. This group confirmed that LBBB is a 'complex electrical disease' involving several anatomic locations and levels of activation delay within the LV, and further described that those patients with LBBB and a QRS duration of less than 150ms had a more homogenous pattern of activation as compared to those similar patients with a QRS duration >150ms. This more homogenous pattern was associated with a normalised trans-septal conduction time and a different location of LV breakthrough site, located further away to the functional line of block²⁸. Non-contact endocardial mapping studies have revealed further underlying inhomogeneity of the depolarisation pattern encompassing the coronary sinus²⁹. RV activation sequence remains unchanged in patients with LBBB, although activation time is prolonged³⁰.

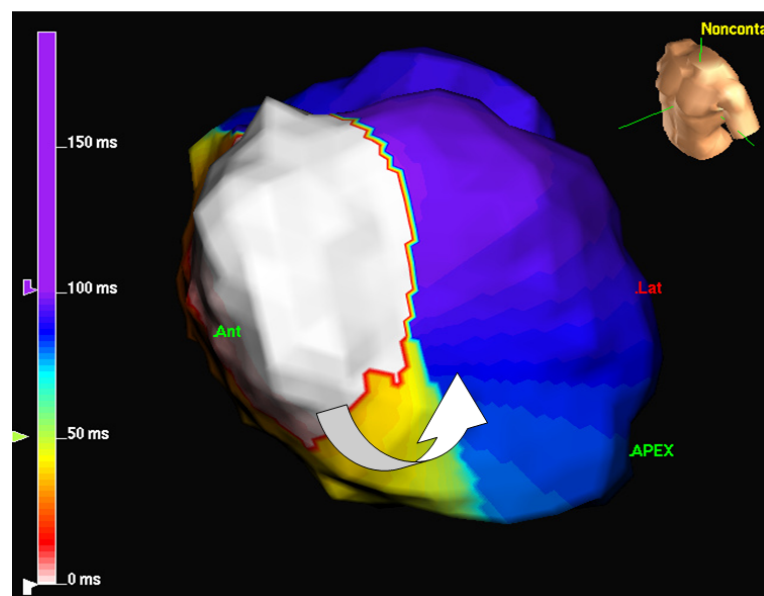


Figure 6: Isochronal map illustrating LBBB in the left ventricle of a patient with ischaemic heart disease. The activation wavefront is seen migrating from the anterior (Ant) to the posterolateral (Lat) wall of the ventricle rotating around a line of functional block illustrated by the crowded isochrones on the anterolateral wall. The timing sequence is initiated from the onset of the QRS on surface ECG. It takes at least 90msec for the activation wavefront to migrate to the lateral wall.

In the presence of RBBB (Figure 7), RV activation is delayed with breakthrough occurring after LV breakthrough via trans-septal conduction from the left side. There appears to be similar overall delay in LV activation in the presence of RBBB as seen with LBBB³¹.

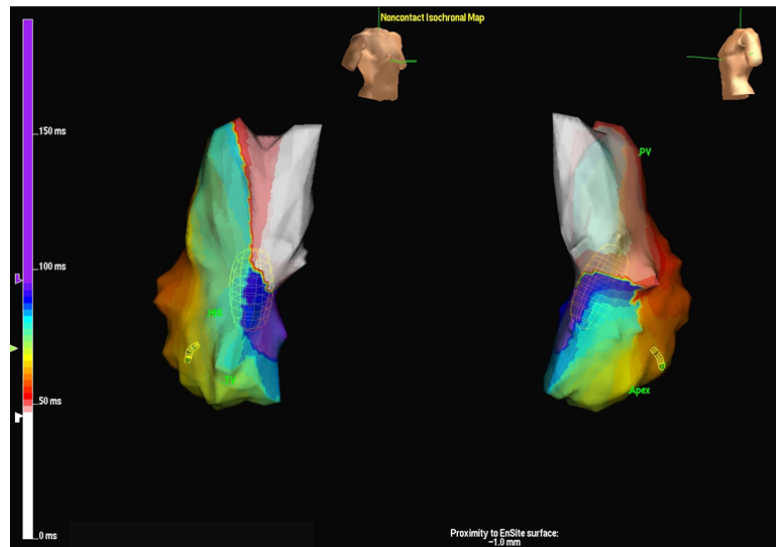


Figure 7: Isochronal map illustrating right bundle branch block as seen in a structurally normal heart. Right ventricular activation is delayed in right bundle branch block, with breakthrough occurring after left ventricular breakthrough via trans-septal conduction from the left side.

2.2.2 Congenital Heart Disease

In describing a functional line of block in patients with LBBB, whose location and length can not only vary between patients but can also be significantly ameliorated with pacing, Auricchio and colleagues studied only patients with dilated cardiomyopathy, less than 30% of whom had coronary artery disease as a cause of disease²⁸. This is relevant as often it is those with ischaemic cardiomyopathy who suffer transmural scarring and by extension, fixed lines of block. Bleeker *et al* found that patients in whom a posterolateral transmural scar was identified by cardiac magnetic resonance imaging did not respond to conventional CRT despite having no other significant difference in entry criteria for delivery³². This is particularly significant when the role and application of CRT are being transferred to any patients with CHD.

Less information exists regarding the electrical activation sequence in patients with CHD. It varies widely according to underlying anatomy and effects of previous palliative or reparative surgery. RBBB occurs frequently and is often iatrogenic, secondary to cardiac surgery³³. Horowitz and co-workers described pre-operative RV activation (without RBBB) preceding LV activation in a conventional manner. Post-operatively, three levels of block to the right bundle were found (proximal, distal and terminal), each associated with a particular approach to surgical ventriculotomy^{34,35}. Although all these levels of block manifest different electrical activation sequences on electrophysiological mapping, all are represented by the same RBBB pattern on the

surface ECG. These fixed levels of block, apparent post surgical repair in patients with CHD, would suggest that the blind transfer of CRT would impart no significant value to the congenital patient.

It is important to note that increases in ventricular volumes and pressure can also induce QRS prolongation over time³⁶. RBBB resulting from ventriculotomy during repair of ToF for example, broadens further during follow-up in association with pulmonary regurgitation (PR) and increases in RV size³⁷. Depolarisation and repolarisation abnormalities in this population are in turn predictive of life-threatening arrhythmias, particularly with a QRS duration greater than 180ms³⁸.

Patients undergoing surgical pulmonary valve replacement (PVR) for significant PR in ToF demonstrate significant subsequent improvements in RV end diastolic volume (EDV)^{39,40}, despite this however, evidence for improvement of electromechanics in this cohort remains contradictory^{41,42,43}. Percutaneous pulmonary valve implantation (PPVI) is an established minimally invasive procedure that can provide an alternative to surgery in selected patients. This procedure is unique in that it permits the study of the effect of reductions in RV volume on electrical remodelling, independent of surgical incision in the ventricular myocardium, additional surgical intervention at the time of valve replacement or cardiopulmonary bypass. Published data have confirmed that this mode of relief of pulmonary outflow obstruction and/or regurgitation, as with its surgical counterpart, does lead to reductions in RV EDV, RV end systolic volume (ESV) and RV systolic pressure^{44,45,46}.

The pressure loaded systemic RV is also often associated with a RBBB pattern to the surface ECG and it may be that the electrophysiological compromises suffered over time may also be resolved by correcting underlying progressive haemodynamic lesions.

2.3 Mechanical dyssynchrony

Abnormal electromechanical interactions may result in dyssynchrony of such magnitude so as to translate to a measurable reduction in cardiac output, independent of the total systolic function of all contracting segments. In a heart compromised by inadequate systolic function the addition of mechanical dyssynchrony can result in a further fall in cardiac output – dyssynchrony generates marked regional heterogeneity of both function and loading of myocardium. Consequently LBBB^{47,48,49} and RBBB⁵⁰ have both been associated with higher morbidity and mortality in patients with acquired HF. Arrhythmia and progressive heart failure are also the leading causes of death in patients with CHD^{2,4} and, in keeping with the finding of increased heterogeneity of activation with increasing prolongation²⁸, QRS duration also relates to worse prognosis in such cohorts^{51,52}. A

potential cause of arrhythmogenicity in the setting of mechanical dyssynchrony, even in the absence of underlying HF, has been proposed by Spragg *et al* who describe regional ventricular electrophysiological remodelling, most marked in the lateral LV wall in adult dogs with LBBB⁵³. Disparities in intraventricular action potential duration (APD) and conduction velocity between the lateral and anterior LV wall may comprise part of a set of unfavourable conditions which together, predispose to a lethal pro-arrhythmic substrate.

2.3.1 Mechanical dyssynchrony in CHD

Several investigators have described the presence of mechanical dyssynchrony in both the right and left ventricles in patients with repaired ToF, often in association with RBBB. Using long-axis M-mode echocardiography, Uebing *et al*⁵⁴ found that, with respect to the RV, the free wall and outflow tract exhibit the greatest delay in activation and overall RV ejection time is prolonged. Using tissue Doppler echocardiography Abd El Rahman describe delayed activation of the LV in around half of patients with repaired ToF and RBBB⁵⁵. The pattern differed from that seen in patients with dilated cardiomyopathy and RBBB, affecting the ventricular septum and not the lateral LV wall. In a recent retrospective analysis of 75 patients with repaired TOF, Tzemos and co-workers noted a significant associated between QRS duration and adverse LV volume, activation delay and septal strain⁵⁶. In contrast, Friedli *et al*, in a more limited study, found delayed RV apical activation in children with TOF and RBBB but no LV activation delay⁵⁷.

Taken together these findings suggest that in the presence of RBBB, mechanical dyssynchrony occurs not only within the RV but can also be found in the LV in adults with repaired ToF. This electromechanical interaction between the two ventricles may be an important, if somewhat poorly understood, aspect of ventricular underperformance and clinical outcome in CHD.

The phenomenon of ventricular interdependence may be relevant in this scenario. Certainly the impact of RV intervention on the LV in adults with ToF has not been extensively studied, however the Toronto group recently published their investigation into this cohort of patients undergoing surgical correction of clinically important PR. They describe a significant improvement in LV function at 1.5-3.5 years following intervention, unrelated to either preoperative RV volumes or degree of RV remodelling, proposing a 'ventricular-ventricular interaction'⁵⁸. It is therefore entirely possible that the chamber-specific ventricular remodelling that would be expected to accompany RV cardiac resynchronisation therapy (CRT) would also beneficially impact the LV. This has yet to be studied in detail.

2.3.2 Pacemaker-related dyssynchrony

Mechanical dyssynchrony can be observed during cardiac pacing, particularly when the heart is activated from the RV apex, during which LBBB develops. The deleterious impact on LV function resulting from RV apical pacing is well documented^{59,60} and appears to be proportional to the overall pacing burden⁶¹ and underlying function of the LV⁶². Stimulating the RV from alternative sites may abrogate iatrogenic dyssynchrony^{63,64,65} although pacing the LV via the cardiac veins remains the gold standard technique for avoiding this complication and indeed reducing dyssynchronous contraction.

The possibility of pacemaker-related mechanical dyssynchrony of the unpaced/sub-aortic ventricle should therefore be considered in patients with CHD. Piran *et al* found that 68% of adults with a single or systemic right ventricle and overt HF had a permanent pacemaker and in those that had succumbed with heart failure, 62% were paced⁶⁶. Janousek and colleagues go further, describing mechanical dyssynchrony associated with single site ventricular pacing as the commonest reason (77% of total) for upgrade to CRT in a large cohort with structural or congenital heart disease⁶⁷. The same authors have described 'LV-induced RV dyssynchronisation' in a group of patients with a systemic right ventricle receiving sub-pulmonary left-ventricular pacing⁶⁸. They suggest that such an approach (akin to RV apical pacing in the structurally normal heart) is deleterious, exacerbating mechanical dyssynchrony in the presence of pre-existing RV systolic dysfunction.

3. Cardiac Resynchronisation Therapy

Cardiac resynchronisation therapy (CRT) refers to the use of permanent pacing systems to stimulate myocardium usually subject to delayed activation, correcting, to a greater or lesser extent, mechanical dyssynchrony. CRT can improve cardiac output and other measures of cardiac function, and has proven very effective at alleviating symptoms of HF and improving survival in acquired heart disease^{69,70}.

CRT devices tend to have three pacing leads, traditionally placed at the right atrium, right ventricle and coronary sinus (lateral LV wall) (Figure 8). Atrio-ventricular and inter ventricular synchrony can thus be optimised in an attempt to improve global cardiac function via electrical pre-excitation of late contracting areas. CRT is sufficiently effective that it has been incorporated into therapeutic guidelines for the management of refractory heart failure: both the American Heart Association and the United Kingdom's National Institute for Clinical Excellence recommend CRT to reduce morbidity and mortality in patients in New York Heart Association (NYHA) class III-IV with symptoms, despite optimal medical therapy and who have a reduced ejection fraction (LVEF<35%) and QRS

prolongation $\geq 120\text{ms}$ ^{71,72}. In patients for whom standard biventricular pacing is not technically feasible, dual site RV pacing has also shown promise⁷³.

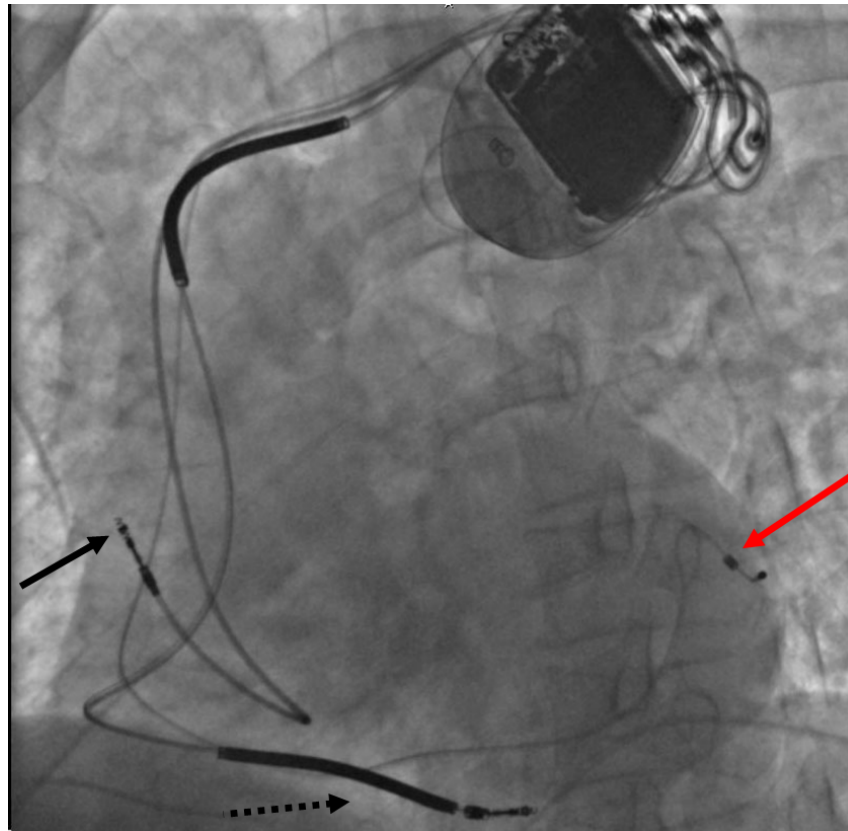


Figure 8: Diagram showing traditional lead placement for CRT. Optimisation of therapy is undertaken subsequent to implantation via echocardiographic guidance. Source: <http://knol.google.com/k/-/IAmNkcMc/I3szpw/biv.png>, embedded from <http://knol.google.com/k/gregory-marcus-md-mas-facc/pacemakers/IAmNkcMc/EOUWRA>; author Gregory Marcus, MD, MAS, FACC

3.1 Cellular basis of function of CRT

Mechanical dyssynchrony alters the loading of the affected myocardium such that the area of early activation has a lesser load than the later activated, and therefore stretched, opposite wall. These latter regions are subject to pre-stretch and therefore work at higher loads, requiring greater energy⁷⁴. CRT negates these effects by increasing homogeneity of LV myocardial activation, specifically by shortening APD in the lateral LV wall⁷⁵, and consequently ensuring more equal loading throughout the LV, enabling a more efficient pump.

Studies have confirmed that LBBB induces regional increases in LV wall mass as a consequence of this phenomenon⁷⁶: Application of resynchronisation therapy to such hearts has revealed normalisation of wall mass with time. Examination of these events at genetic levels finds that LBBB is associated with increased local expression of genes coding for stretch, remodelling and cell

regeneration contributing to myocardial hypertrophy. Subsequent biventricular stimulation in these hyper-productive systems results in a reversal of this over-expression within only a few months⁷⁷, and is also associated with reduced apoptosis⁷⁸. At the cellular level, up- and down-regulation of various calcium, sodium and potassium channels are thought to mediate changes in local cell reactivity, both to exacerbate heterogeneity of APD in LBBB, and in most cases, to restore it following CRT. The specific mechanism behind these findings remains controversial however⁷⁹.

3.2 CRT in right bundle branch block

The vast majority of patients with acquired heart failure and QRS prolongation have LBBB. Less is known about the effectiveness of CRT in the presence of RBBB, underrepresented in clinical trials, though interest is growing in this area⁸⁰. In animal studies Byrne and colleagues found less mechanical dyssynchrony for the same degree of LV dysfunction and QRS prolongation with RBBB compared to LBBB⁸¹. The authors also describe a blunted effect of CRT on improving LV synchrony in those with RBBB, establishing that conventional atrioventricular RV pacing was at least as efficacious as biventricular CRT in this group. This latter finding may be relevant in patients with CHD and RBBB in whom sub-pulmonary RV dysfunction is the principal electromechanical problem.

Closer scrutiny of those patients with RBBB who have undergone CRT insertion would suggest that outcome is inferior compared with their counterparts with LBBB^{82,83,84}. It is interesting to note however, that symptomatic improvement is noted⁸². Regardless, the small numbers with RBBB and the probable differences in underlying pathophysiology (predominantly RV disease) and requirements for/at optimisation of delivery, dictates that this remains a matter for further study. No clear criteria based on directly observed measures or patterns of mechanical dyssynchrony have been consistently found to distinguish responders from non-responders amongst patients with acquired heart disease^{85,86}. The evidence base for helping select patients with CHD for CRT is even smaller. Some have suggested that as many as 9% of unselected patients with a systemic RV are potential candidates for CRT based on conventional CRT trial entry criteria⁸⁷. The use of published guidelines on patient selection for CRT (systemic ventricular ejection fraction ≤ 0.35 , QRS >120 ms, sinus rhythm, NYHA class III or IV^{71,72}) seems a pragmatic approach. Care should then be taken to document baseline and outcome data in order to enhance the evidence base.

3.2 CRT in CHD and subpulmonary RV dysfunction

As the outflow tract (RVOT) and free wall of the RV show latest activation in patients with repaired ToF⁵⁴ these sites intuitively constitute targets for lead placement when delivering CRT. Rigorous

testing of this hypothesis is lacking however. The different electrophysiological consequences of surgical intervention and disease progression over time would infer that specific and standard CRT lead placement in all patients would not necessarily generate a positive outcome. Indeed, conventional lead positions have been shown to provide excellent clinical response: Kirsch and colleagues report that, in a child with repaired ToF presenting with heart failure, upgrading a dual chamber pacemaker with epicardial RVOT lead to a biventricular device with an RV apical lead provided the best haemodynamic and symptomatic response⁸⁸.

Dubin *et al* studied the acute haemodynamic effects of RV pacing in 7 patients with CHD (6 with repaired ToF), all of whom had RBBB and RV dysfunction and determined that atrioventricular pacing resulted in significant haemodynamic improvement⁸⁹. Leads were positioned at the apex, RVOT or ventricular septum and the greatest increase in cardiac index was associated with the narrowest paced QRS duration.

AV delay optimisation would also appear important when pacing patients with sub-pulmonary RV dysfunction. Stephenson *et al* found that in patients with repaired ToF, RV apical pacing with AV delay optimisation produced a significantly narrower QRS duration than RV apical pacing without such programming⁹⁰. By optimising AV delay immediately post-operatively Janousek and co-workers improved electrical and haemodynamic parameters⁹¹ in children with conduction delay with further enhancement with inter/intraventricular resynchronisation.

Acute improvements in central haemodynamics can therefore be achieved using standard univentricular pacing in these groups. The potential benefits of this approach should not be outweighed by iatrogenic dyssynchrony in the sub-aortic LV, especially if the systolic function of this chamber is impaired. Nonetheless, this approach raises the tantalising prospect of using “sub-pulmonary RV CRT” to improve RV performance and clinical endpoints in outpatient populations.

A recent prospective study from France examined the effects of stand alone RV pacing and biventricular stimulation in eight patients with repaired ToF (RV apex only) and 12 surgically created swine models (RV apical, lateral or anterior wall)⁹². In these animal models, biventricular stimulation was associated with improved LV and RV dP/dt (n=7) as measured invasively, compared with RV pacing alone. A further five animals underwent electroanatomic mapping and a significant decrease in dyssynchrony was found with biventricular pacing as measured by echocardiography. The eight adults studied with repaired TOF all had RV dysfunction, QRS prolongation and a measure

of pulmonary regurgitation. Biventricular stimulation resulted in improvements in both RV and LV dP/dt compared to sinus rhythm ($p < 0.05$), though RV activation alone also decreased RV dP/dt. QRS duration was noted to broaden from baseline with RV pacing, but decreased when biventricular pacing was applied. These patients did not undergo electroanatomic mapping and LV function was not defined. This latter is relevant given that the superiority of biventricular pacing over stand alone RV pacing described suggests possible associated LV impairment. Further, there is no evidence to suggest that RV apical activation was delayed with respect to the rest of the RV myocardium. Future studies to elucidate electrical activation at the RV and target delivery are necessary, as well as delineating between those with associated LV dysfunction.

Several studies have also confirmed that across all patient groups with CHD, including those with ToF, surgery is linked to a decrease in ventricular contractile function, most marked on the second post-operative day⁹³. A sub-group of patients with ToF also have a significantly poorer post-operative course, linked to a restrictive cardiac physiology, requiring longer intensive care recovery with prolonged inotropic support⁹⁴. The application of acute, temporary, CRT in these patients would also be beneficial should appropriate targets be found for delivery.

4. Outcome in CHD: The rationale for risk stratification

Morbidity and mortality statistics for adults with CHD necessarily differ between the heterogeneous anatomical cohorts studied. Even within similar physiologic substrates, different surgical techniques and ongoing advances further dictate that outcomes will vary. Regardless, it is established that compared to their age-matched healthy peers, adults with CHD suffer significantly higher burdens of morbidity and premature death: This is greatest in those with a single ventricle and in those in whom the morphologic RV is in the systemic position, such as in TGA.

In this latter population, HF and SCD are the leading causes of demise, with the average age at death placed at a tragically young 27 ± 7 years⁴. A recent long-term follow-up study found that HF accounted for 38% of deaths in patients with TGA, and SCD 30% of deaths⁵. Despite this there is very little evidence to identify those at risk, or guide the timely use of therapeutic strategies for either mode of demise as compared to those available in patients with acquired and cardiomyopathic heart disease. Further, despite objective measurements of sub-maximal exercise capacity and evidence of cardiac dysfunction on echocardiographic and magnetic resonance imaging, it is common to encounter patients at all levels of CHD who subjectively feel well and define themselves as asymptomatic. This suggests that reliance on symptoms, as is frequent in clinical

practice, in selecting those at high risk of SCD and HF events may neglect an important, and possibly large, group of patients who would benefit from early and targeted therapeutic intervention.

4.1 Definition and Incidence

4.1.1 Heart Failure

Heart failure is a syndrome with systemic implications in which the heart is unable to supply sufficient blood flow to meet the demands of the body. It is a common condition in the general population, affecting 2% of adults, and 6-10% of those aged over 65 years⁹⁵. In the western world, the commonest causes are ventricular dysfunction (through ischaemic or other cardiomyopathy) and hypertension. Extensive research into the pathophysiology of HF has led to improved treatment options and decreased mortality: The use of β -blockers and angiotensin-converting enzyme inhibitors specifically, have improved survival by decreasing both sudden deaths and progressive HF deaths. CRT, as discussed, has revolutionised device therapy of HF. Several evidence based guidelines exist for the diagnosis and treatment of HF in those without congenital heart disease both in Europe^{96,97} and the United States⁹⁸.

In patients with CHD, HF can be acute or chronic. The underlying cause tends to be varied and often multifactorial. Most often acute HF occurs in the post-operative period in children and adults following either primary repair, palliative surgery or other later surgical interventions. Studies suggest that those anatomies requiring greater surgical intervention (such as ventricular septal defect repair over atrial septal defect) are associated with the greatest post-operative impairment of ventricular myocardial systolic performance due to greater intra-operative trauma⁹³. On occasion however, it is surgery that is required to alleviate HF in those with very complex anatomy, as in hypoplastic left heart syndrome. Acute post-operative HF, though far from benign, is often transient and ventricular function does improve.

Chronic HF is a pervasive disease in CHD; it has been proposed that CHD in fact forms the quintessential HF syndrome⁹⁹, fulfilling as it does several criteria for diagnosis, including structural cardiac abnormality, neurohormonal activation and objective exercise intolerance. HF may result from dysfunction of either the left or right ventricle, whether these latter be subpulmonary or systemic in nature, or both^{55,56}.

Smaller population numbers contributes to a paucity of data in determining factors that predict HF death in the CHD population: Currently, methods of HF prognostication are taken from evidence gathered in those with acquired or cardiomyopathic heart disease – few are tested in the adult CHD population.

4.1.2 Sudden Cardiac Death

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes which occurs within one hour of the onset of symptoms in a person with known or unknown cardiac disease. It accounts for at least half of all causes of cardiovascular mortality in the United Kingdom. It is an important cause of death in HF, and ischaemic heart disease is the most prevalent aetiology in adults¹⁰⁰. Although mortality increases with increasing severity of symptomatic HF, rates of sudden death are greatest in those with mild to moderate HF¹⁰¹.

Although medications, in particular β blockade, can significantly ameliorate risk, the introduction of the implantable cardioverter defibrillator (ICD) revolutionised outcomes in those at risk of SCD. As in the general HF population (without CHD), there exists a broad evidence base to guide identification, risk stratification and therapeutic options in those at risk of primary or secondary sudden cardiac death¹⁰².

In CHD, in particular adults with a systemic RV, SCD is often due to malignant tachyarrhythmia¹⁰³. Predicting which patients are at risk of such arrhythmias remains elusive – in clinical practice, the majority of patients with ICDs are those in whom it was given for secondary prevention. The use of ICD's in this way has, mainly, been extrapolated from ischaemic and dilated cardiomyopathy literature; ICD's for primary prevention has a less clear-cut transfer value.

Evidence from patients with repaired ToF suggests that there may be easily measured surface ECG markers that predict risk in terms of malignant arrhythmia and SCD, including prolonged QRS duration and QRS, QT and JT dispersions³⁸. This is in the context of a subpulmonary RV however; early research in patients with a systemic RV has found that similar abnormalities may be relevant yet this data is somewhat contradictory and spans different age and palliation cohorts^{104,105,106,107}.

4.2 Investigative tools and predictors of outcome

4.2.1 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is a tool for the non-invasive assessment of the function and structure of the cardiovascular system. It is derived from and based on the same basic principles as magnetic resonance imaging but is optimised for use in the cardiovascular system: This principally involves the use of ECG gating (where image acquisition is triggered by the R wave) and rapid imaging sequences. Images can be acquired in several different planes, including coronal, axial and sagittal and are presented in the short axis view, four and two chamber views, as still images or cines. CMR imaging can provide information on cardiac function and morphology, myocardial viability and perfusion, and flow and velocity through various structures. Advances in spatial and temporal resolution and increased imaging speed has ensured that CMR has become one of the most valuable diagnostic tools for heart disease.

Although echocardiography and X-ray guided catheterisation remain vital and valuable clinical tools for the investigation of cardiovascular disease, CMR imaging is now being used in many centres and with increasing frequency, for the diagnosis and follow-up of paediatric and adult patients with CHD^{108,109}. CMR provides a powerful investigative tool, giving morphologic and haemodynamic information that echocardiography and catheterisation alone do not provide: Extracardiac anatomy, including the great arteries, systemic and pulmonary veins, can be delineated with high spatial resolution, in any imaging plane, irrespective of body habitus. Vascular and valvular flow patterns and volumes can be assessed¹¹⁰, shunts can be quantified¹¹¹ and myocardial function can be measured accurately and with high reproducibility¹¹², regardless of ventricular morphology. Finally CMR surpasses both catheterisation and echocardiography in providing high resolution, isotropic three dimensional data sets (Figure 9). This allows for reconstruction of data in any anatomical imaging plane, giving complete visualisation of complex congenital cardiac anomalies without the use of ionising radiation.

The asymmetric morphology of the RV, the anterior location of the ventricle and the coarse endocardial trabeculations renders echocardiographic assessment of this chamber difficult. CMR is currently the gold standard imaging method of accurately assessing RV volumes and ejection fraction¹¹³. However there remains much inter-centre variation in the specific post-processing methods by which to measure the ventricle after imaging, and no universal, standardised method has yet been agreed¹¹⁴.

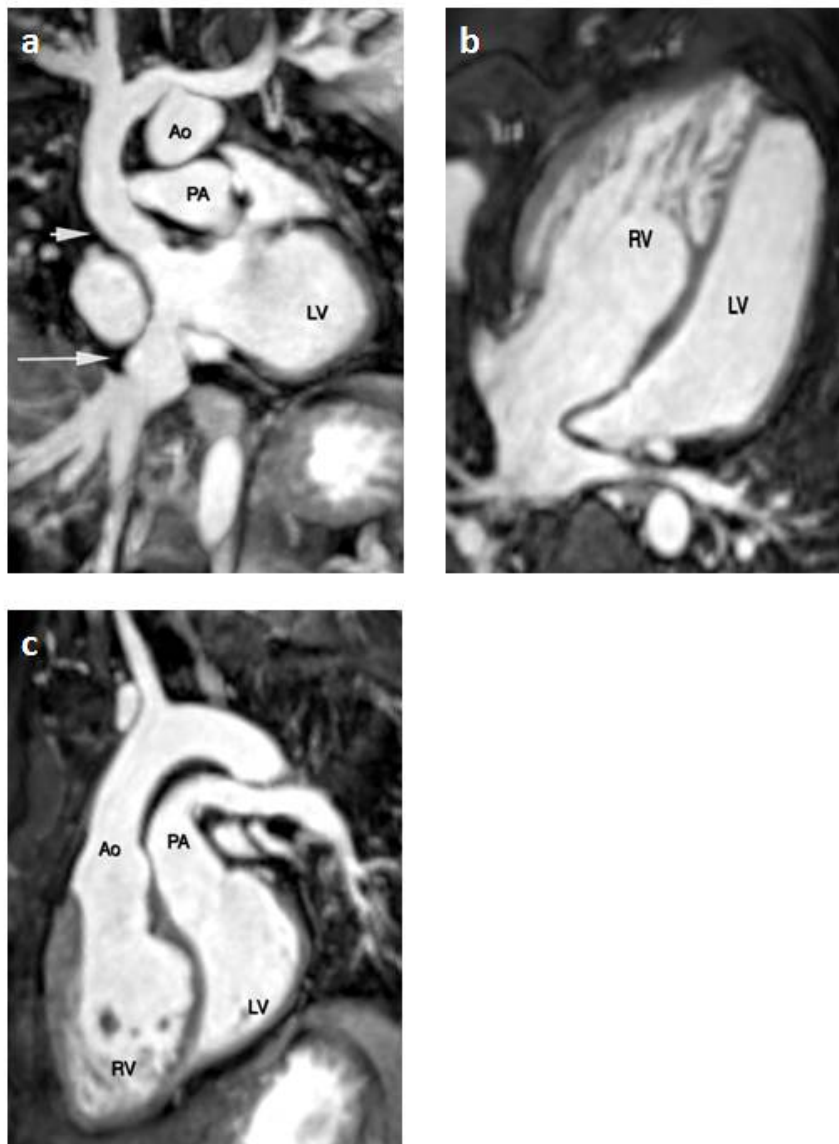


Figure 9: These are images of a typical adult patient late after the Senning procedure for TGA. The images are created from data acquired using the 3D “whole-heart” sequence. This image data is a white blood sequence, with data acquired in isotropic voxels, during the diastolic phase of the cardiac cycle. This enables multiplanar reformatting in any plane and allows detailed morphological analysis. These images are thin maximal intensity projections in 3 planes:

- a) Through the superior and inferior caval baffles (*short and long white arrows, respectively)
- b) Through the ventricles, in a 4 chamber view, and showing the pulmonary venous connection to the RV.
- c) Through the ventricles in the outflow tract view, showing the aorta arising from the morphological RV and the pulmonary artery arising from the LV.

Ao = aorta, PA = pulmonary artery, RV = morphological right ventricle, LV = morphological left ventricle.

Long-term outcome in adults with atrial switch palliation of TGA is known to relate to the function of the systemic RV¹⁶. Despite being the most accurate and reproducible tool for assessing this, CMR

imaging is time consuming and availability is often restricted to specialist centres and specialist operators. Moreover, referral tends to be prompted on clinical grounds in a population of patients who notoriously underreport symptoms and functional ability¹¹⁵. In addition, there is a high prevalence of implanted pacing/defibrillator devices in this population and the small but significant proportion of patients with claustrophobia can also limit its use. The development and validation of surrogate clinical markers that relate to ventricular function as determined by CMR would consequently be highly desirable.

4.2.2 Electrocardiography

Electrocardiography is a simple, cheap and easily reproducible tool frequently available in the outpatient setting. It is a painless investigation that records potential differences between defined sites on the body surface that vary during the cardiac cycle, providing information about heart rate and heart rhythm, as well as several other parameters of repolarisation and depolarisation.

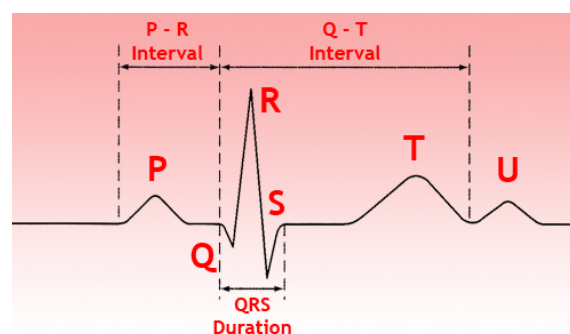


Figure 10: Traditional measurements on the surface 12 lead ECG. Image courtesy of Heart Rhythm Guide, © 2013

Several defined parameters exist that are routinely measured on a 12 lead ECG (Figure 10), the commonest being QRS duration, QTc and PR intervals. In the general, healthy, population these parameters have so-called 'normal' ranges as follows:

PR interval: 120-200ms

QRS duration: <110-120ms

QT interval: <420ms (Corrected QT interval determined by dividing the QT interval by the square root of the preceding R-R interval).

These surface ECG parameters have been associated with both risk of malignant arrhythmia and adverse outcome, in terms of HF and SCD. These parameters, and others, are well established in the

general adult population; however, their relevance, value and associated relationships in the those with CHD as yet remains to be fully elucidated.

4.2.2.1 QRS Duration

QRS duration is a measurement of ventricular depolarisation, and prolongation of this parameter beyond 120ms is, as already intimated, associated with adverse outcome: In the Framingham cohort, longer QRS duration was related to an increased risk of later HF development¹¹⁶ as well as increased LV wall mass and decrease in LV systolic function¹¹⁷. QRS duration is an established predictor of all cause mortality¹¹⁸, including SCD¹¹⁹, and prolongation of this parameter has been incorporated into guidelines for application of device therapy for HF^{71,72}.

Within the CHD population, the most extensively studied cohort are those with repaired ToF. Gatzoulis *et al* describe a significant risk of death and malignant tachyarrhythmias in those with QRS duration >180ms⁵¹, and in this substrate QRS duration is related to increasing RV EDV associated with progressive PR; in some cohorts QRS duration has been found to shorten with successful haemodynamic correction⁴³ – though this is not a universal finding^{41,120}. All cohorts so far studied with this substrate have undergone surgical correction of PR, and it is possible that concurrent myocardial stunning and injury suffered at the time of surgery affects this outcome variable: The availability of percutaneous intervention to correct pulmonary valvular insufficiency or stenosis provides an excellent opportunity to study the electrical effects without the added confounding affects of surgery. It might be expected that if QRS duration relates to risk of ventricular arrhythmia, then correction of an aggravating haemodynamic pathology might ameliorate this risk – this has yet to be positively verified⁴².

Schwerzmann and colleagues describe an increased rate of death in those with a QRS>140ms and previous Mustard palliation of TGA¹⁰⁵; however, other studies have not described any difference in QRS duration in those who suffered a SCD versus those who did not with similar palliative operation^{106,107}.

4.2.2.2 QRS dispersion

QRS dispersion (QRSd) is the measurement obtained when subtracting the narrowest QRS duration in any of the 12 leads from the broadest. Whilst still an indicator of ventricular depolarisation, QRSd provides information concerning the heterogeneity of this event, but is not routinely measured as

part of the 12 lead examination. QRSd has been found to be associated with LV systolic function¹²¹, and with increased risk of sudden death^{122,123}.

In adults with ToF, the association of a QRS>180ms with a prolonged QRSd (>35ms) was determined to be a highly specific and sensitive marker of identifying those at risk of sustained ventricular tachycardia. Certainly in adults with both ToF and TGA, QRSd was found to increase with time of follow-up³⁶; however, no further studies have as yet, been undertaken to ascertain relationship of this parameter with other variables, or indeed further consolidate predictive risk.

4.2.2.3 QT interval

The QT interval is defined as the interval from the onset of the QRS complex (onset of ventricular depolarisation) to the end of the T wave (end of ventricular repolarisation) and as such is an indicator of ventricular depolarisation and repolarisation. Measurement is usually corrected for heart rate, and presented as QTc. Prolongation of QTc interval >500ms is associated with risk of malignant ventricular arrhythmia, specifically *torsade des pointes*, and subsequent possible degeneration to ventricular fibrillation.

In those with genetic abnormalities, most notably long QT syndrome, QTc prolongation is an established risk factor for malignant arrhythmia and SCD. In such high-risk families, QTc prolongation can be profound, and the underlying pathology due to ion channel dysregulation.

In those without a genetic basis for disease, QTc interval prolongation tends to be less excessive. Certainly medications can cause problems, specifically some anti-arrhythmics, anti-histamines and antibiotics, and several have been withdrawn as a result (Cisapride). In the general population; however, with HF and/or ischaemic heart disease, the relevance of QTc prolongation to risk remains unclear: the UK-HEART study from the end of the last decade looked at 500 patients followed up for an average of 2 years, and determined no relation of QTc interval to risk of progressive HF, SCD or all cause mortality¹²⁴. A subsequent qualitative overview of 7 prospective studies found QTc interval to not be a reliable indicator of future risk, even in those with established cardiovascular disease¹²⁵. However, when prolongation occurs alongside an elevated BNP >400pg/mL in those with established HF, QTc interval becomes a strong independent predictor of risk¹²⁶.

There is very little literature regarding QTc in those with CHD. Certainly Roos-Hesselink and colleagues¹⁶ found that QTc interval did not prolong with long-term follow up in adults with Mustard

palliation of TGA. Kammeraad *et al* found no significant difference in QTc interval in similar adults who had suffered a sudden death compared to those that had not¹⁰⁷. Both studies involved small cohort sizes; further study will be necessary to establish whether this parameter carries any prognostic information.

4.2.2.4 QT dispersion

QT dispersion (QTd) is the difference between the QT interval at its maximal and least duration across all 12 ECG leads. It is an indirect measure of inhomogeneity of ventricular repolarisation¹²⁷ and is associated with both frequency of ventricular ectopy post acute myocardial infarct¹²⁸, incidence of ventricular tachycardia and fibrillation¹²⁹ and mortality in HF¹²². In a large prospective study of American Indians, QTd was found to be a significant predictor of all-cause and cardiovascular mortality in univariate Cox analysis¹³⁰.

Its role as a marker or substrate for arrhythmogenesis remains controversial however¹³¹, and it does not yet form a routine part of surface ECG assessment¹³². As a marker of heterogeneity of myocardial repolarisation however, and as such a potential marker of underlying malignant tachyarrhythmia, QTd measurement remains an important and widely used research tool. Normal values are generally quoted as being between 30-60ms^{133,134,135}.

As a marker of risk in CHD, several studies have positively linked QTd to malignant arrhythmia and outcome in both ToF¹⁰³ and TGA^{106,52}; however, these results have not been consistent with Kammeraad and colleagues finding no significant difference in QTd in those with TGA that suffered a SCD compared to those whom had not¹⁰⁷. Further research is required to establish whether this measurement of repolarisation heterogeneity can indeed provide valuable prognostic information.

4.2.2.5 JT dispersion

JT dispersion (JTd) is the difference between the maximal and minimal JT durations across a 12 lead ECG. Less literature exists on this parameter, again, not routinely used in ECG assessment. As another marker of heterogeneity of repolarisation, it has also been linked to risk of malignant tachyarrhythmias¹³⁶; in children with long QT syndrome, JTd >55ms was linked with risk of ventricular tachyarrhythmias¹³⁷. Increased JTd has also been associated with hypertension and LV wall mass¹³⁸.

Gatzoulis and co-workers also studied this parameter and found that when >65ms in association with a QRS >180ms it was highly specific and sensitive in determining risk of sustained VT³⁸.

4.2.3 N Terminal-pro Brain Natriuretic Peptide

Neurohormonal activation characterises the chronic heart failure syndrome¹³⁹. Several systems exist to combat the pathophysiological consequences of heart failure, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, the kallikrein-kininogen-kinin system, the vasopressinergic system, the natriuretic peptide systems and endothelin. Of these, the natriuretic peptide system has been most extensively studied.

NT-pro Brain Natriuretic Peptide (NT-proBNP) is a 76 amino acid protein synthesized and released into the circulation by the ventricular myocardium in increased quantities under conditions of cardiac haemodynamic stress. It is an inactive protein, cleaved from its precursor pro-BNP, and co-secreted alongside its active cousin, BNP (Figure 11). The half-life of NT-proBNP is 1.5 to 2 hours versus 20 minutes for BNP. The physiologic actions of natriuretic peptides include lowering systemic vascular resistance and central venous pressure, and increasing natriuresis, thereby causing a decrease in both blood volume and cardiac output.

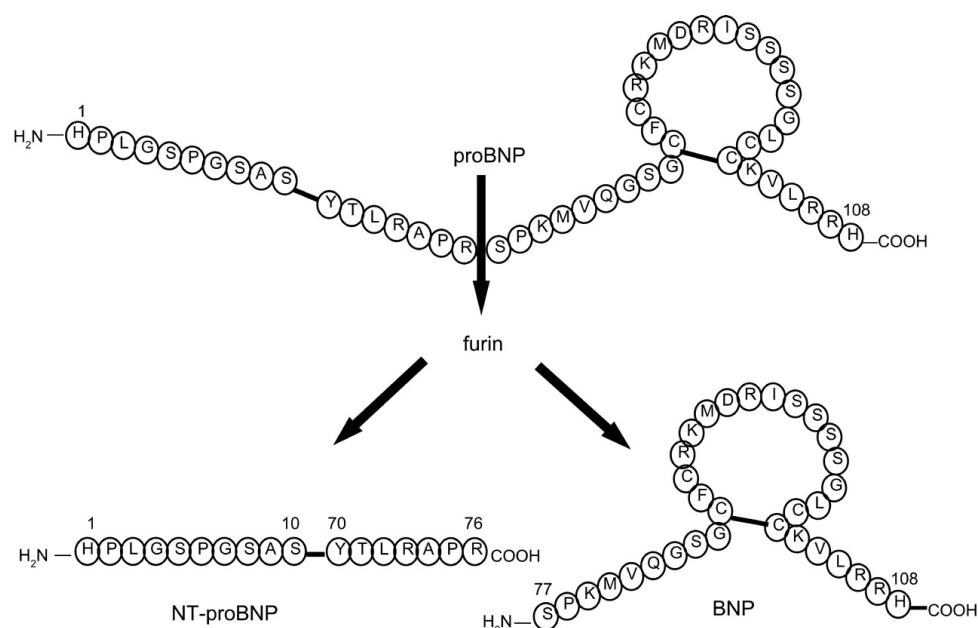


Figure 11: ProBNP cleaved into (inactive) NT-proBNP and (active)BNP. Image from Hall C Eur J Heart Fail 2004;6:257-260. Copyright © (2014) by permission of Oxford University Press

In acquired and cardiomyopathic heart failure, BNP is a reliable predictor of all cause mortality and/or HF admission. It has an established role in detecting asymptomatic left ventricular dysfunction in high risk populations¹⁴⁰, predicting cardiovascular events in those with preserved ventricular function¹⁴¹, and providing prognostic information with serial measurement¹⁴². BNP levels correlate with modalities commonly used for HF diagnosis and monitoring of disease progression^{143,144,145}. Further, BNP has a major role in excluding left ventricular dysfunction and HF in those in whom there is diagnostic doubt, leading to the incorporation of this haemodynamic marker into European guidelines for HF diagnosis⁹⁶. Further, a meta-analysis of published literature concluded that BNP is also a powerful indicator of SCD and risk of malignant arrhythmia, independent of reduced LV ejection fraction¹⁴⁶.

BNP levels have been found to correlate significantly with increasing age and decreasing creatinine clearance. Although levels are generally consistently higher in females than males, a significant difference between the two genders has not been established.

In mixed cohorts of patients with CHD, BNP has been shown to relate to systemic ventricular function as determined by echocardiography (Figure 12)¹⁴⁷ and to function of the pressure overloaded systemic and sub-pulmonary RV as determined by CMR¹⁴⁸. The role and applicability of BNP in adults with a systemic RV, specifically TGA corrected by atrial redirection surgery, has had early, encouraging results^{149,150}: BNP levels have been shown to relate to the severity of tricuspid regurgitation and RV volume overload following Mustard and Senning surgery^{149,151,152}; Tulevski and colleagues included 9 patients with TGA palliated by Mustard or Senning procedure in a heterogeneous group and found that RVEF, measured by CMR, correlated negatively to BNP levels ($r = -0.65$)¹⁴⁸; Garg and co-workers found no correlation between RVEF and BNP in patients with systemic RV physiology, although there was a strong correlation with atrial natriuretic peptide (ANP); a somewhat surprising result as both ANP and BNP correlate exceptionally closely ($r = 0.91$, $P < 0.0001$) in adults with congenital heart disease¹⁵³.

Although similar relationships between BNP levels and RV volumes have also been described in the context of sub-pulmonary RV anatomy¹⁵⁴, Neffke *et al* found only a weak correlation between BNP and RVEDV in a heterogeneous cohort with systemic or subpulmonary RV physiology³⁶ suggesting that the pathophysiological responses may differ between settings and should perhaps be investigated in isolation. The relation of BNP to functional capacity and parameters of RV function remain to be elucidated however.

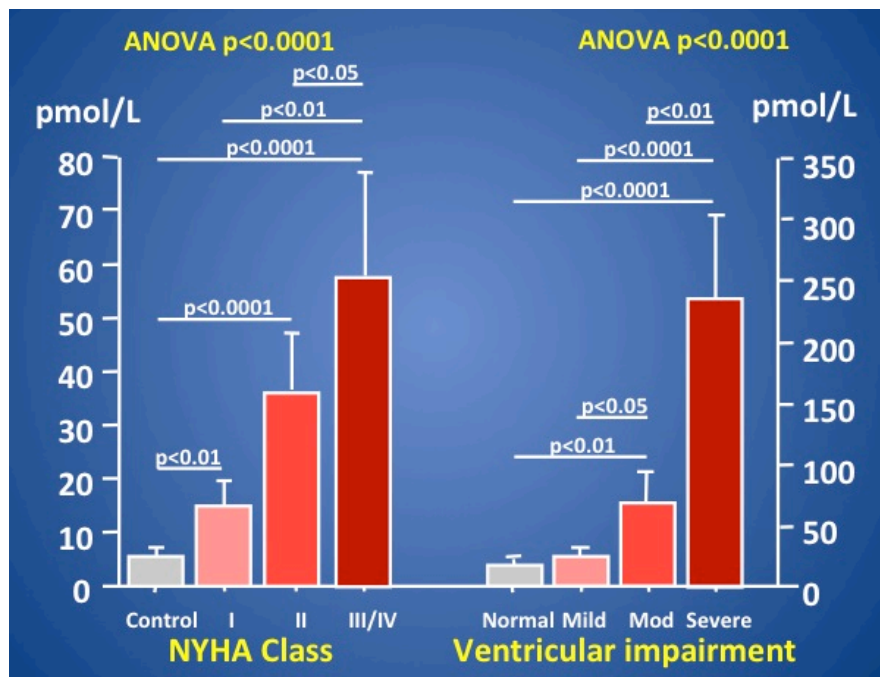


Figure 12: BNP levels according to NYHA functional class and systemic ventricular impairment in patients with CHD. Image courtesy of Aidan Bolger

4.2.4 Cardio Pulmonary Exercise Testing

Cardio Pulmonary Exercise (CPEX) testing is a stress test that simultaneously assesses cardiac and respiratory function, including gas exchange at the cellular level. During the CPEX, continuous 12 lead ECG monitoring enables examination of myocardial ischaemia and arrhythmia, as well as determination of heart rate response and variability. Exercise is undertaken on a treadmill or cycle ergometer and a gas mask is fitted for the duration. Computerised breath-by-breath analysis allows quantification of oxygen uptake (VO_2), carbon dioxide output (VCO_2) and determination of the anaerobic threshold. Outcome measures are scored against age and gender matched controls and recorded as a percentage of the predicted outcome.

CPEX testing is an established tool in pre-operative risk assessment, routinely used to determine cardiorespiratory fitness in select patients prior to major surgery. In those with established or early HF it is used to determine clinical status as well as for risk stratification: Peak VO_2 levels of less than 14ml/min/kg are predictive of a less favourable outcome, independent of other clinical and haemodynamic findings^{155,156}. In addition, the ventilatory response to exercise, defined as the relation between carbon dioxide production (VCO_2) and minute ventilation (VE), also relates to outcome in HF, providing supplemental information in addition to peak VO_2 ¹⁵⁷.

There has recently emerged an early evidence base for all cause mortality among adults with CHD: In patients with repaired ToF peak VO_2 and VE/VCO_2 slope were found to be independent predictors for adverse cardiac events¹⁵⁸, and peak VO_2 recently found to be prognostic in those with Ebstein's anomaly¹⁵⁹. In a cohort of noncyanotic patients, Dimopoulous *et al* determined that those with a VE/VCO_2 slope >38 had a higher risk of dying within two years (13%) than those who did not (1%)¹⁶⁰. Colleagues from the same institution previously published their finding that a peak VO_2 cut-off of $<15.5\text{ml/kg/min}$ was associated with a 2.9 fold increased risk of admission or cardiac death compared to those who achieved a peak $\text{VO}_2 >15.5\text{ml/kg/min}$ ¹⁶¹. Giardini and colleagues studied adults with a systemic RV and previous Mustard or Senning palliation and proposed a VE/VCO_2 slope cut-off >35.4 as being predictive of four year mortality or cardiac related admission. In this study however, VE/VCO_2 slope was related to the age of the patient undertaking the test, and also age at original palliation¹⁶². Given that RV function deteriorates with age at follow-up, then their results are perhaps not surprising but do provide a quantitative target. Further useful data on exercise testing including observation and calculation of heart rate reserve and chronotropic index (ChI). Both have been found to provide prognostic and predictive outcome data in general cohorts with CHD and in those with a systemic RV^{161,161,163}.

CPEX testing is a highly reproducible investigation, incorporated into both general HF and adult CHD guidelines^{95,164}; however, it suffers a number of potential disadvantages; it can be a time-consuming and expensive investigation not readily available outside of tertiary centres. It is hence not routinely applicable as a rapid diagnostic test in an ambulatory setting of a HF clinic despite being a valuable diagnostic and prognostic tool.

At my study institution, CPEX testing certainly forms part of the clinical repertoire in following up patients, including those with TGA. However, despite objective measurements of sub-maximal exercise capacity and evidence of cardiac dysfunction on echocardiographic and CMR imaging, it is common to encounter patients who subjectively feel well and define themselves as asymptomatic^{115,165}. This suggests that reliance on symptoms, as can occur in clinical practice, in referring patients for further investigations may disregard those who would benefit from early and targeted therapeutic intervention.

4.2.5 Quality of Life Assessment

The Minnesota Living with Heart Failure Questionnaire (MLWHFQ) is a 21 question self assessment tool that measures the effects of symptoms, functional limitations and psychological distress on an

individual's quality of life (Appendix A). The questionnaire is primarily used as a research tool in adults with acquired heart failure; however, it is a valid and reliable indicator of the impact of the disease on a patients' quality of life¹⁶⁶.

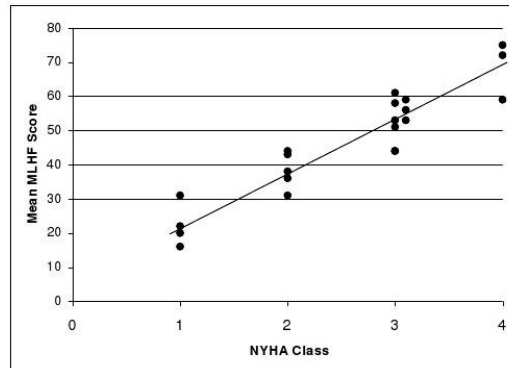


Figure 13: Taken from 'Overview of the Minnesota Living with Heart Failure® Questionnaire' by Thomas Rector showing the relationship between reported self assessment and clinical assessment of functional status by NYHA Class.

The MLWHFQ provides the clinician with a subjective assessment of function, enabling recording of day-to-day limitations and psychological impact of disease as compared to the more widely used but objective method of capacity, the New York Heart Association classification.

Although this questionnaire has not been validated for use in patients with CHD, it is however, a simple and straightforward means of assessment that is highly portable and inexpensive to use. As such it will be included in this study and comparison made with other diagnostic and prognostic markers.

AIMS & OBJECTIVES

The aims of this research are twofold: Firstly to examine the electromechanical interactions occurring in the right ventricle in adults with congenital heart disease, both directly via electroanatomic mapping, and indirectly via measurement of surface electrocardiographic parameters. Subsequently, this Thesis will study the electromechanical consequences of altering RV electrical activation directly by targeted pacing of this chamber, or by correcting underlying RV anatomic pathophysiology in isolation.

Secondly, this Thesis will undertake an analysis of current status and functional ability in those with a systemic right ventricle in order to understand and develop a practical characterisation of disease severity in this cohort. Parameters validated in the general population without congenital heart disease as being predictive of risk and outcome will be applied to this substrate and include neurohormonal, electrocardiographic and imaging tools. The interrelationships between these markers will be studied.

The hypotheses of this research are therefore:

1. There are significant changes in measurable surface electrical parameters following isolated correction of abnormal haemodynamics.
2. There are significant changes in cardiac haemodynamics with targeted dual-site RV pacing.
3. There is a significant relationship between surface electrical measurements and various neurohormonal and imaging markers of heart failure status.
4. Diffuse myocardial fibrosis as a novel imaging biomarker is present in significantly greater quantities in the ventricles of those with a systemic right heart compared to normals.
5. The clinical characteristics of adults with a systemic right ventricle are significantly related to other measures of cardiac functional status.

MATERIALS AND METHODS

3.1 Electroanatomic mapping

Electroanatomic mapping of the electrical activation sequence of the RV took place on previously consented patients intraoperatively, following completion of the surgical procedure. All patients had been rewarmed and were off cardiopulmonary bypass. All were haemodynamically stable, in sinus rhythm, and remained under general anaesthesia.

- i. A unipolar electrode (Convenience 6494, Medtronic, Mn, USA) was placed at the anatomical RV apex and the metallic sternal retractor used as a unipolar reference.
- ii. A second roving unipolar electrode was sequentially placed at preselected locations on the epicardial surface of the RV as determined by a 9-point grid system where the RV apex was point 9 (Figure 14).
- iii. Unipolar electrograms were recorded at 1000Hz (LabSystem™ PRO EP Recording System, Bard Clearsign™, Bard Inc, MA, USA). The fastest downstroke of the unipolar electrogram (dV/dt min) was taken as local activation and times of roving activation were taken in comparison to local activation at the apex.
- iv. Unipolar pacing electrodes were then fixed to the RV apex and at the latest activation as determined by electrophysiological mapping.
- v. Two further atrial leads were placed as per usual by the operating surgeon prior to the insertion of two chest drains and closure of the midline sternotomy in the usual fashion.

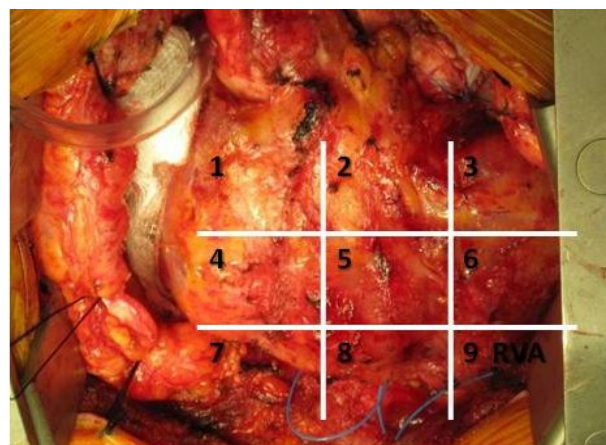
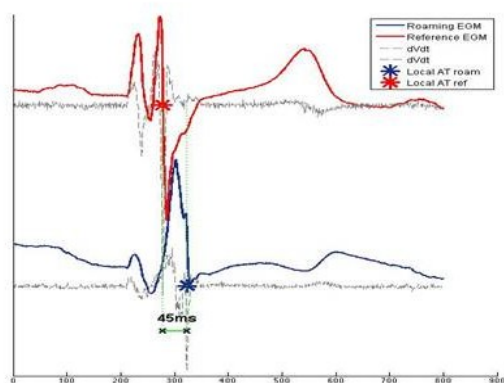


Figure 14: Pictorial representation of the exposed RV surface (right) with 9 preselected areas to guide surgical placement of the epicardial electrode. The left panel shows a representation of the roaming and reference EGM with determination of activation of onset.

3.2 Acute haemodynamic study

This was performed in all consented patients within three hours of surgery ending. In all cases, patients were haemodynamically stable, off inotropic support and remained under general anaesthetic on the Intensive care unit. There were no pacing related complications.

- i. Invasive haemodynamic monitoring was available via an arterial line; the Edwards Flotrac System¹⁶⁷ (already in use on the intensive care department) uses peripheral arterial waveform analysis to present continuous measures of cardiac output (CO), cardiac index (CI), stroke volume (SV), and mean arterial pressure (MAP) from which baseline and study measurements were derived. The device was set up and monitored pre-, intra- and post-operatively.
- ii. A patient return electrode was attached to the patient's lateral chest wall and connected to the pacing device to correct for unipolar pacing leads.
- iii. An atrial epicardial pacing wire was connected to the atrial port of the external pacing device (SJM 3085 dual chamber temporary pacemaker) and the ventricular epicardial pacing wires were connected as necessary so as to subsequently generate DDD RV (apical), DDD RValt or DDD BiRV pacing.
- iv. Pacing order was determined using an online random sequence generator for each individual patient, and further randomly repeated at each site three times to take into account normal physiologic changes that may occur during the study period. A return to baseline was allowed between each period of pacing. Pacing was programmed to each site for at least 30 secs (max 1 min) as Flotrac interprets over 20 seconds of continuous data.
- v. In addition, two different AV delays at 20 msec and 40 msec less than patients own intrinsic PR interval were programmed at each site. Pacing was repeated at each of the RV sites (single and dual) for duration 30 secs to 1 minute for these two AV delays. Haemodynamic effects to be monitored via the Edwards' Flotrac system as above with return to baseline between pacing periods.
- vi. For each pacing mode an ECG was obtained for later analysis of electrocardiographic indices.

Therefore (in random order):-

AAI

AAI

AAI

DDD RV with AV delay minus 20 ms

DDD RV with AV delay minus 40 ms

DDD RValt with AV delay minus 20 ms

DDD RValt with AV delay minus 40 ms

DDD BiRV with AV delay minus 20 ms

DDD BiRV with AV delay minus 40 ms



Total number of pacing cycles – 21 –
with a return to baseline between
each cycle

3.3 Sub-acute echocardiographic study

On post-operative day 3 or day 4, patients were again assessed but on this occasion under echocardiographic guidance and with a conscious patient. There were no pacing-related complications. Baseline echocardiography (without pacing) was performed first as follows by the same operator (JO'L):

Left ventricular function

- i. Apical 4 chamber: Tissue Doppler of septal and lateral mitral annulus
- ii. CW Doppler Aortic flow (apical 5 chamber) and LV outflow tract diameter in parasternal long-axis view for stroke volume.
- iii. Measure mitral inflow

Right ventricular function

- iv. Apical 4 chamber: Tissue Doppler of lateral tricuspid annulus.
- v. Continuous wave (CW) Doppler Pulmonary flow and RVOT diameter in parasternal short-axis view.
- vi. Measure tricuspid inflow
- vii. Pulmonary VTI
- viii. Tricuspid regurgitation jet measurements for RV dp/dt ¹⁶⁸
- ix. Determine severity of mitral and/or tricuspid regurgitation (affects stroke volume calculations).

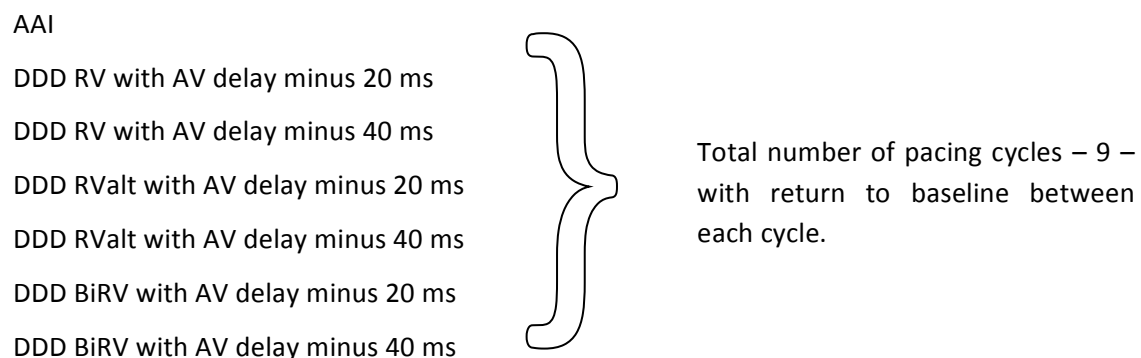
AV delay optimisation

- x. Determine LV filling time – pulsed wave Doppler of mitral inflow
- xi. Aortic VTI – CW Doppler of Aortic flow (trace area)

Epicardial pacing wires were connected to the external pacing generator as described above and all pacing modes again undertaken randomly. A patient return electrode was again necessary to compensate for the unipolar temporary pacing wires.

Pacing was delivered as previously described and lasted long enough to complete the echo protocol (approximately 3-4 minutes). On this occasion, pacing cycles were only delivered once – there were no repeats.

Therefore (in random order):-



Temporary pacing wires were removed as deemed clinically necessary on day 4 or 5.

3.4 Electrocardiography

Twelve lead electrocardiograms (ECG) were undertaken throughout this Thesis. The settings of each ECG were identical for each patient (paper speed 25mm/s). These standard original hard copies were then scanned for online analysis using the CardioCalipers program (Version 3.3 for Windows, Iconico, New York, www.iconico.com), which enabled magnification for greater measurement accuracy.

QRS duration was averaged for each ECG following analysis of all 12 leads, and defined as the first positive/negative deflection to the last sharp positive/negative deflection across the isoelectric line. QRS dispersion (QRSd), QT dispersion (QTd) and JT dispersion (JTd) were calculated by subtracting the narrowest interval from the longest across any 12 leads. The end of the T wave was defined as the point of return to the isoelectric line. QT intervals were averaged across the 12 leads for each ECG and corrected for heart rate to obtain QTc.

3.5 Blood testing

Peripheral venous blood samples were obtained from all participants after they had rested for at least 20 minutes. Blood was collected into tubes containing EDTA/aprotinin and lithium/heparin. NT-pro brain natriuretic peptide (NT-pro BNP) samples were centrifuged at 3000 rpm for 15 minutes at 4°C and immediately analysed via sandwich immunoassay using electrochemiluminescence (E 170 Module, Roche Diagnostics, Basel, Switzerland). For all subjects, renal function was determined using routine laboratory methods.

3.6 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPEX) was performed on an electronically braked ergometer cycle (Lode, Groningen, Holland) with computerised breath by breath ventilator gas analysis (MedGraphics, Minnesota, USA). Prior to exercising, height and weight were measured and all sensors calibrated.

Patients wore a full face mask connected to an expiratory limb pneumotachograph, allowing sampling of mouth tidal PCO₂ and PO₂. 12-lead ECG was recorded at rest, continuously during exercise and into recovery.

Patients were encouraged to exercise to full capacity on an incremental bike protocol. Workload increased at 15-25 Watts depending on underlying fitness level; however, the ramping protocol included an initial loadless three minutes of cycling to allow equilibration. Criteria for ending the test included clinical need, or patient exhaustion having aimed for or achieved a respiratory exchange rate >1.01. A period of active recovery (slow pedalling) followed maximal exertion. Cuff blood pressure was checked every two minutes, and transvenous oxygen saturations were measured continuously via a probe positioned over the right supraorbital artery.

Peak oxygen uptake (VO₂), anaerobic threshold (AT) and ventilatory response to CO₂ production (VE/VCO₂) were derived from the respiratory gas analysis during maximal exertion. VE/VCO₂ was measured as the ratio at the AT. In turn, AT was determined by using the modified V-slope method. CHI was calculated as has been previously described:

$$= \frac{(\text{peak HR} - \text{resting HR})}{(220 - \text{age} - \text{resting HR})}$$

An ECG taken at peak exercise was also scanned for online analysis to determine QRS duration, QRSD, QTd, JTd and QTc as stated above.

3.7 Cardiac Magnetic Resonance Imaging

Patients with devices or other metallic implants did not undergo this investigation.

Cardiac magnetic resonance (CMR) imaging was performed using a 1.5Tesla scanner (Avanto, Siemens Medical, Erlangen, Germany) at one institution (GOSH). All scans were analysed and reported by one person experienced in this cohort of patients (MH) who followed a set protocol for each scan.

Patients were formally consented and underwent measurements for height and weight. Intravenous cannulation at the left antecubital fossa enabled later injection of contrast agent (Dotarem® 279.32mg/ml, Gadoteric acid, Guerbet, France) during imaging. ECG monitoring took place throughout the scan.

3.7.1 Assessment of Ventricular Volumes and Function Using Cine MRI

Retrospective gated steady-state free precession cine MRI's of the heart were acquired in the vertical long-axis, 4-chamber view and the short-axis view covering the entirety of both ventricles (9 to 12 slices). Image parameters were TR=2.2 ms; TE=1.1 ms; flip angle=78°; slice thickness=6 to 8 mm; matrix=192×312; field of view=300 to 380 mm; and temporal resolution=25 phases acquired during a single breath-hold. Assessment of LV and RV volumes was performed by manual segmentation of short-axis cine images at end diastole and end systole (Argus; Siemens Medical Systems). End diastolic and end systolic volumes were calculated by use of Simpson's rule for each ventricle, and from these volumes, stroke volume (SV) and ejection fraction (EF) were calculated. Cardiac output (CO) was calculated by multiplying the effective arterial forward flow by the heart rate.

3.7.2 MR Flow Quantification

Pulmonary artery and aortic flow data were acquired by use of a flow-sensitive gradient-echo sequence (TR, 27 ms; TE, 3.2 ms; flip angle, 30°; slice thickness, 5 mm; and matrix, 256×240) during free breathing. Image planes were located at the midpoint of the main PA and just above the sinus level of the ascending aorta. Through-plane flow data (30 phases per cardiac cycle) were acquired by use of retrospective cardiac gating. Arterial blood flow was calculated from phase contrast images by use of a semiautomatic vessel edge-detection algorithm (Argus; Siemens Medical Systems) with operator correction. All volume and flow measurements were indexed for body surface area and expressed in mL/beat/m².

CHAPTER 4: Right Ventricular electrical remodelling

4.1 Introduction

Sudden cardiac death constitutes one of the leading causes of death in all patients with CHD, often secondary to malignant cardiac arrhythmias^{4,5}. A significant association between the risk of arrhythmic death and a variety of surface ECG parameters, including QRS duration, QRS, QT, and JT dispersion (d) has been shown in patients with repaired ToF^{38,51}. In this subset of patients there is an established correlation between increasing right ventricular (RV) end diastolic volume (EDV) and QRS duration over time^{37,51,55} secondary to progression of pulmonary regurgitation (PR). This finding is not limited to those with a subpulmonary RV and has been found in patients with systemic RV and chronically elevated RV pressures. In these patients, RV end diastolic volumes correlated with QRS duration and both this and QRSd significantly increased during follow-up³⁶.

Surgical pulmonary valve replacement (PVR) is associated with a reduction in RV EDV in adults with severe PR^{39,40,169} and research suggests that this leads to a reduction in QRS duration⁴³. This implies that reductions in RV volume, and presumably RV wall stress, lead to electrophysiological remodelling when chronic RV dilatation is reversed.

Percutaneous pulmonary valve implantation (PPVI) has been shown to be a safe and feasible treatment option for RV to pulmonary artery conduit dysfunction⁴⁶, and is not subject to the confounding effects of open-heart surgery, including cardiopulmonary bypass^{44,170}. PPVI represents a pure model for studying the haemodynamic consequences of RV stretch. It is associated with positive outcomes and avoids incisions in the RV which could promote further conduction block and re-entrant ventricular tachycardia. Follow-up of patients has revealed significant improvements in RV EDV and RV systolic pressure in patients with either PR or outflow tract obstruction⁴⁵. In this study, I investigated changes in ECG parameters (QRS duration, QTc, QRS/QT/JT dispersions) following PPVI, and their relationship, if any, to RV EDV and RV systolic pressure.

4.2 Methods

4.2.1 Study population

Ninety nine patients were included in this prospective study. All had underlying CHD with haemodynamically significant pulmonary valve lesions and underwent PPVI at Great Ormond Street

Hospital, The Heart Hospital or Harley Street Clinic (London). All had undergone previous surgical palliation or repair.

PPVI occurred between May 2001 and July 2007 enabling at least one year follow-up in all subjects. Clinical and morphologic inclusion criteria for PPVI include: RV systolic pressure $>2/3$ systemic with symptoms, RV systolic pressure $>3/4$ without symptoms, moderate to severe PR with either, symptoms, severe RV dysfunction or dilatation, or impaired exercise capacity¹⁷¹. RVOT diameter measurements had to be less than 22x22mm and greater than 14x14mm.

4.2.2 Electrocardiogram

ECGs recorded 24h pre-, 24h post and 1 year post PPVI were analysed. Electric intervals, including QRS duration, QTc interval and QRS/QT and JT dispersion were calculated as set out in the earlier methods section. Inter-observer differences were compared with an independent observer who was blinded in a similar manner to a series of 20 sample study ECG's. Inter-observer differences between measured electrical parameters was $<2.5\%$.

4.2.3 Echocardiography

Pre- and 1 year post-operative echocardiography reports were reviewed. Images were obtained using a Vivid 7 (GE Vingmed, Milwaukee, Wis) by operators experienced in scanning CHD patients who followed a set protocol for each patient. RV systolic pressure (RVSP) was calculated from continuous wave Doppler analysis of the tricuspid regurgitant jet¹⁷². 16% (n=16) had no discernable TR jet and were not included in this analysis; 89% of patients underwent 1-year follow-up echocardiography.

4.2.4 Cardiac magnetic resonance (CMR) imaging

CMR imaging was performed using a 1.5T scanner (Symphony or Avanto, Siemens Medical System, Erlangen, Germany). Patients underwent scans prior to the procedure and at 1-year post-procedure. In 17 patients (17%) CMR data were not acquired due to pacemaker or automated implantable cardioverter defibrillator insertion (12%) or scan intolerance (5%). CMR assessment of ventricular volumes and function has been previously described^{44,170}.

For the purpose of this study, PR was defined quantitatively via CMR as a regurgitant fraction of more than 25%, PS was defined as an RV outflow velocity of greater than 3.8m/s with a regurgitant fraction of less than 25%, and mixed lesions comprised the remainder. The 17 patients not able to

undergo MR imaging had valve lesion severity assessed qualitatively by echocardiography and/or angiography.

4.2.5 Statistical analysis

Data are presented as mean \pm standard deviation. Student's paired or unpaired t-test or repeated measures ANOVA were used to analyse the data where appropriate. Repeated measures ANOVA were followed by Fisher's PLSD post-hoc analysis, all t-tests with Bonferroni correction as necessary. Linear regression analysis was used to ascertain any relationship between ECG parameters and RV volume. A p value <0.05 was considered significant. Statistical analysis was performed using StatView statistical software (SAS Institute Inc, North Carolina, USA) and all graphs produced using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, USA,).

Statistical analysis comprised examination of the group as a whole, and was then subdivided according to the pulmonary valve lesion (PR, PS, mixed) and underlying structural pathology.

4.3 Results

4.3.1. Patient characteristics

Ninety nine patients were identified for inclusion to this study. Mean age at time of procedure was 23.1 ± 10 years, 60% were male. The commonest pulmonary valvular lesion was predominantly stenotic (43%), followed by mixed (29%) and then predominantly regurgitant (27%). The most common congenital diagnosis within the group was pulmonary atresia with ventriculoseptal defect (32%) followed by repaired ToF (28%). Others included transposition of the great arteries (11%), common arterial trunk (12%), congenital aortic or pulmonary valve disease (13%) and double outlet right ventricle (3%). No patients died during follow-up.

4.3.2 Electrocardiographic data

Mean pre-procedure QRS duration was prolonged at 137 ± 29 ms with no significant change at any time point in the total group (24 hour 133 ± 28 ms, 1 year 134 ± 29 ms; $p=0.7$) (Figure 15a). The subgroup of patients with a pre-procedure QRS duration ≥ 150 ms also showed no significant change in global or praecordial lead QRS duration either immediately, at 24h or 1 year post PPVI (162 ± 9 ms, 159 ± 12 ms, 160 ± 12 ms; $p=0.28$) (Figure 15b).

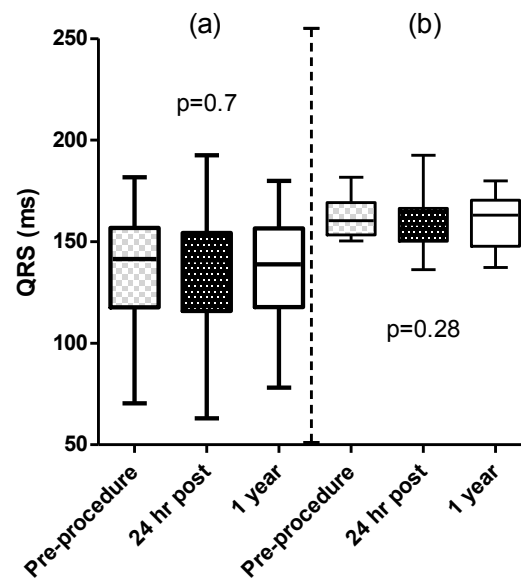


Figure 15: No significant change in either total group QRS duration (a) or in those with pre-procedure QRS > 150ms (b) at any time point during follow-up.

When QRS duration was assessed by underlying pulmonary valvular lesion, there was a significant reduction in the predominantly regurgitant group at one year (135 +/- 27 to 128 +/- 29ms; $p=0.007$) (Figure 16). Patients with underlying PS or mixed valvular lesions showed no significant decrease in QRS duration.

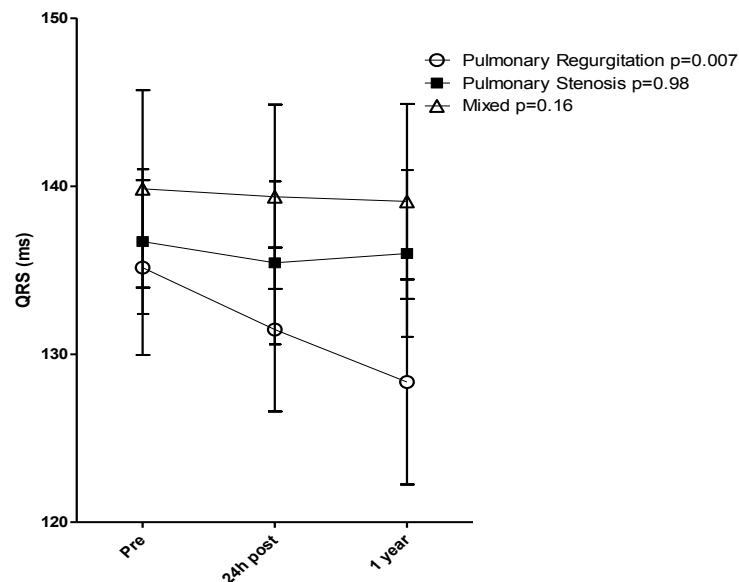


Figure 16: Changes in QRS duration with follow-up within the pulmonary valve lesions. The PR group show a significant difference at one year ($p=0.007$).

In the whole group, QTc, QTd, QRSd and JTd shortened significantly at 1 year ($p \leq 0.001$) (Figure 17). All 4 of these parameters were prolonged immediately post procedure (JTd and QTd achieving statistical significance - $p=0.04$; $p=0.002$) prior to shortening (Figure 18).

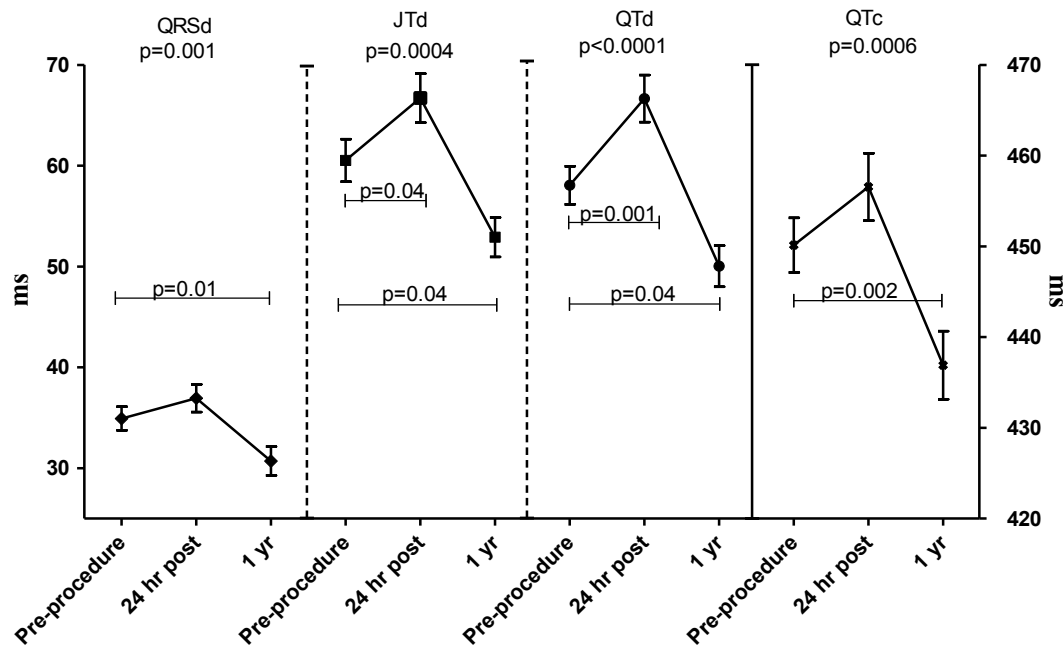


Figure 17: Total mean values with standard error bars for QRS, JT and QT dispersions (left axis) and QTc (right axis). Both JTd and QTd show significant increases immediately following PPVI.

When comparing patients according to valve lesion, those with obstructive lesions had a significant improvement in all dispersion values at one year compared to those with predominantly regurgitant or mixed lesions (Figure 18). QTc was significantly lower at 1 year in both the PR (450 ± 30 to 435 ± 36 ms) and PS (448 ± 31 to 433 ± 26 ms) groups ($p=0.02$ for both).

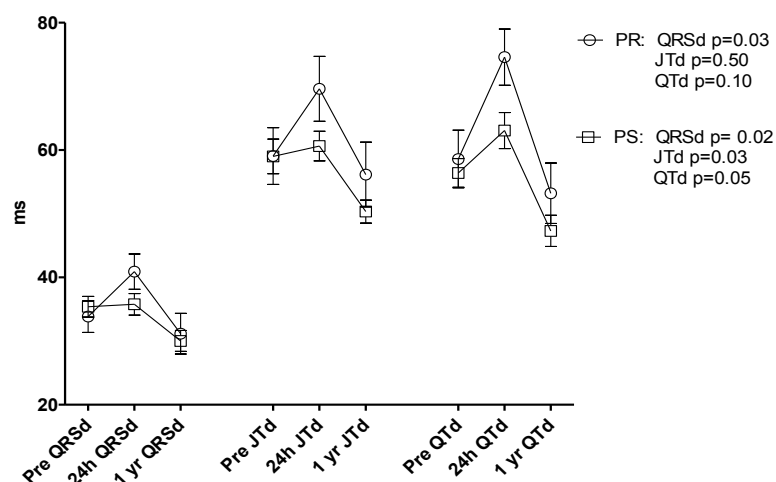


Figure 18: Dispersion values in the obstructive and regurgitant groups. Obstructive lesions show significant changes at one year.

There was no significant difference in any of the ECG parameters within the different underlying congenital diagnoses.

4.3.3 Echocardiographic data

Echocardiographic determination of RV systolic pressure revealed significant reductions 1-year post PPVI in all patients (66.3 \pm 22.7 mmHg to 51.7 \pm 18.6 mmHg; p <0.0001, Table 1). When this is broken down to underlying lesion type, those with predominant stenosis had the greatest reduction in pressure both acutely (76.2 to 54.4 mmHg; p <0.0001) and at 1 year (76.2 to 57.8mmHg; p =0.0004).

4.3.4 Cardiac magnetic resonance

Indexed RV EDV and RV end systolic volume (ESV) decreased significantly across the whole group at 1 year (-17.7% change, p <0.0001; -12.8%, p =0.0005 respectively, Table 1). There was no significant change in right ventricular ejection fraction (p =0.29). Patients with PR had a significantly higher starting RV EDV than those with PS (111.8 \pm 92.1 and 91 \pm 26 ml/m²; p =0.017); however, their one year values were not significantly different (92.1 \pm 31 and 82 \pm 27ml/m²).

	Pre	1 year	p value
Cardiac magnetic resonance			
End diastolic volume (ml/m ²)	100 \pm 32	87 \pm 26	<0.0001
End systolic volume (ml/m ²)	51 \pm 25	42 \pm 21	0.0005
Right ventricular ejection fraction (%)	51 \pm 13	54 \pm 13	0.29
Trans thoracic echocardiography			
<i>Total cohort</i>	66 \pm 23	52 \pm 19	<0.0001
Right ventricular systolic pressure (mmHg)			
<i>PS</i>	76.2 \pm 18	57.8 \pm 20	0.0004
<i>PR</i>	50.2 \pm 21	44.5 \pm 18	0.24
<i>Mixed</i>	69.7 \pm 18	50.4 \pm 18	0.003

Table 1: Showing pre- and 1 year values for indexed right ventricular volumes, ejection fraction and systolic pressure together with measured statistical significance.

Pre-procedure QRS correlated with pre procedure RV EDV (r =0.34; p =0.002). There was no such correlation at one year; however, RV EDV at one year did correlate with QTc at one year (r =0.4; p =0.007). When analysed by valvular lesion there was a significant correlation at 1 year with change in (Δ) RV EDV and Δ QTd in the PS group (r =0.4, p =0.03). Similarly, Δ RV EDV correlated with Δ QTc (r =0.6, p =0.04) and Δ JTd (r =0.6, p =0.03) respectively in the PR group.

4.4 Discussion

Sudden cardiac death is a leading mode of death in patients with CHD. Arrhythmic death in repaired ToF has been associated with a QRS duration >180ms, and the addition of further electrical measurements (QRSd, QTd, JTd) has further refined this risk^{38,51}. QRS prolongation has been associated with increasing RV EDV^{36,37,55}, and patients undergoing surgical PVR demonstrate significant subsequent improvements in RV EDV. PPVI is an established minimally invasive procedure that may provide an alternative to surgery in selected patients. This procedure is unique in that it permits the study of the effect of reduction in RV volume on electrical remodelling, independent of surgical incision in the ventricular myocardium, additional surgical intervention at the time of valve replacement or cardiopulmonary bypass.

Previous publications have confirmed that this mode of relief of pulmonary outflow obstruction and regurgitation, as with its surgical counterpart, leads to reductions in RV EDV, RV ESV and RV systolic pressure^{44,45,170}. This study therefore aimed to assess the 1 year changes in QRS duration, QTc and QRS, JT and QT dispersion following isolated (percutaneous) pulmonary valve implantation in a cohort of patients with CHD. Given that these electrical parameters can be viewed as a marker of arrhythmia propensity and burden, electrical remodelling could impact positively on these outcomes over the long term.

This study confirms a significant reduction in RV EDV, RVESV and RV systolic pressure following PPVI.

4.4.1 QRS duration

In patients with pulmonary valve pathology who do not undergo PVR, the QRS duration is normally noted to increase yearly by approximately 2-4ms^{36,52}. Several studies have examined the effect of surgical PVR on surface ECG parameters, mainly QRS duration, with inconsistent results: some studies show post procedure shortening^{43,173}, others stabilisation⁴¹, and yet others initial stabilisation followed by subsequent prolongation over time¹²⁰. My study includes a cohort with a number of underlying congenital cardiac diagnoses and either obstructive, regurgitant or mixed pulmonary valvular pathologies. I found that the group as a whole shows no significant decrease in QRS duration at one year of follow-up after PPVI. However, when selecting those patients with predominantly regurgitant physiology, there is a significant reduction in QRS width at one year. This sub-group is comparable to the surgical cohorts since these latter include patients in whom the vast majority have pulmonary regurgitation.

The follow up period of 1 year compares favourably with the surgical cohorts, which vary between a mean of 8 months¹⁷³, 14.3 months⁴³ and >4 years^{41,120,169}. It is important to note that all of the above studies included patients who underwent additional surgical intervention at the time of PVR, a valid confounding factor. Some of these studies found that the greatest degree of QRS length reduction occurred in those in whom the pre-procedure duration was >150ms^{41,173} – I did not find this to be the case in my study.

None of the patients died during the 1 year follow up period. A reduction in QRS duration would be expected to effect a longer-term decrease in arrhythmia propensity and associated mortality^{174,175}; however, very few studies have examined the long-term outcomes in patients undergoing PVR. Harrild and colleagues observed that in 55 of 98 patients with repaired ToF undergoing PVR with available pre- and post-procedure ECG data, not only was there no significant change in QRS duration at a mean of 3 years follow-up, but that there was no survival benefit in terms of death or ventricular tachycardia⁴². Their study cohort attempted to match these patients to a control population with repaired ToF of similar ages and similar QRS durations, although this latter allowed an overlap of 30ms. Such a range of 30ms in paired QRS durations may be misrepresentative, since a difference of such magnitude would represent significant changes in the conduction properties of the ventricular myocardium. It is also relevant to note again that surgical myocardial incisions during PVR could confound the interpretation of any outcome data in these patients.

This study suggests that isolated intervention in patients with pulmonary regurgitation does lead to a reduction in QRS duration at 1 year. It would appear that the underlying physiological process of pulmonary regurgitation, as compared to the high-pressure environment of obstructive lesions, allows for remodelling of depolarisation as manifest on the surface ECG. Longer term follow up will determine whether this change stabilises, continues to reduce or indeed prolongs over time. Assessment of parallel arrhythmic burden will further define the impact of this outcome.

4.4.2 QTc, QRSd, QTd, JTd

This study shows a significant decrease in all the above ECG parameters at one year. Interestingly, there was a trend, statistically significant in the case of JTd and QTd, towards immediate post-procedure lengthening followed by gradual improvement over the course of the year which could not be accounted for by the anaesthetic agents used. Other authors have not found any significant positive changes at follow up when measuring QRSd or QTd following surgical PVR⁴³, indeed Therrien *et al* document a non-significant increase in QTd at one year¹²⁰. It should be noted however, that

these studies included patients in whom pulmonary regurgitation was the predominant lesion. These differing findings may be explained by comparison of pulmonary lesions which found superior electrical (dispersion) outcome in those with obstructive physiology, suggesting that this high pressure physiology is associated with greater reversibility in returning to a more homogeneous form of ventricular repolarisation following its relief. Despite this, and importantly, QTc duration reduces regardless of lesion type.

4.4.3 Cellular correlates of surface ECG measures

QTc, QTd and JTd are all parameters of repolarisation and surrogate measures of regional dispersion action potential duration (APD). It is well recognised that myocardial stretch increases monophasic APD-mechano-electric feedback (MEF). MEF has been demonstrated in a wide variety of experimental preparations and species to cause delayed after depolarisations and either shortening or lengthening of the APD depending on the nature of the intervention. Therefore, MEF can cause triggered activity and generate the appropriate conditions for re-entrant arrhythmias. Gatzoulis *et al* have suggested that the RV distension, secondary to chronic PR, creates an optimal electrophysiologic milieu in which arrhythmias may develop^{38,51}. Penny's group has demonstrated that after only 3 months of PR in the lamb, the RV shows enhanced susceptibility to stretch-induced arrhythmias and increased inhomogeneity of activation¹⁷⁶. Myocardium from these ventricles showed impaired mechanical restitution, increased intracellular resistivity, reduced conduction velocity, increased dispersion of activation, and prolonged endocardial APD. This would create ideal conditions for re-entrant VT, and provide the mechanistic basis for the clinical observation of an increase in QRS dispersion³⁶ and QRS duration⁵² in patients after TOF repair. These changes are thought to accompany progressive ventricular dilation secondary to PR; the rate of which is one of the most sensitive markers for ventricular arrhythmia and sudden death⁵¹. An *in vitro* study comparing dilated and hypertrophied human myocardium demonstrated significantly longer steady-state APD in dilated versus hypertrophied hearts and steeper APD restitution slopes in the latter¹⁷⁷. Therefore, measurable changes in electrophysiological parameters occur in response to volume and pressure overload which may have important clinical implications. The fact that these surface ECG markers of APD are reduced post PPVI suggests that correction of the haemodynamic lesion in this patient cohort results in increased homogeneity of repolarisation which would theoretically translate into a reduced susceptibility to ventricular arrhythmia. This reduced risk of arrhythmia would be further enhanced particularly in the PR group as QRS duration here was significantly reduced, reflecting more homogenous myocardial conduction and less opportunity for conduction

block and re-entry. The advantage that PPVI avoids incisional scars would further serve to reduce the arrhythmogenicity of the RV in these patients.

4.5 Limitations

RV EDV measured in this cohort pre- PPVI is less than that described for other surgical cohorts⁴³; however, my population comprised both children and adults. It should be noted that only those patients with a valve orifice area of 22mm or less are amenable to percutaneous intervention, and this may have some bearing on outcome – it is possible that those with PR and a larger valve orifice area have greater haemodynamic compromise, although all patients are referred for either intervention when similar degrees of RV volume overload are reached. This is unlikely to have been a significant issue in the younger patients. This study was not able to examine changes in arrhythmia propensity, either inducible or spontaneous, and this is an important area for further study.

Finally, the PPVI procedure is a relatively recent interventional strategy. As yet, numbers of patients are small; however, with increasing availability and larger numbers, statistical strength will be increased.

4.6 Conclusions

This study shows that electrical remodelling occurs following PPVI in patients with CHD, with significant haemodynamic and electrocardiographic improvements at 1 year of follow-up. Patients with predominant regurgitant physiology show most marked improvements in the surface ECG parameters of depolarisation, whilst for those with stenotic physiology improvements are most marked in surface ECG parameters of repolarisation. It remains to be seen whether these improvements translate into decreased long-term arrhythmia burden and risk of sudden cardiac death.

Surgical (open) pulmonary valve replacement (PVR) currently remains the commonest means of intervention for pulmonary valve disease in CHD however. This mode of therapy facilitates direct examination of the electrical activating system on the surface of the RV at the time of surgery: Identifying the latest area of activation on the RV surface may provide therapeutic insight into sites for targeted resynchronisation therapy in these complex patients with the potential for direct electrical remodelling. The next Chapter will examine this in greater detail.

CHAPTER 5: Targeted single and dual site right ventricular pacing

5.1 Introduction

Adults with ToF or significant congenital pulmonary stenosis (PS) therefore often have a RBBB pattern on the surface ECG resulting from earlier corrective surgery^{33,34,35}; QRS duration often prolongs during follow-up in association with progressive PR and consequent increases in RV size³⁷. In such adults, QRS duration and other ECG parameters are linked with increased risk of malignant arrhythmias and sudden cardiac death^{38,51}. Further, long-term problems with resulting RV dysfunction also contribute to morbidity and early mortality^{55,178,179} in this group.

Surgical intervention to implant a competent pulmonary valve can cause acute RV dysfunction leading to increased morbidity and mortality in the short term: Studies show that across all patient groups with CHD, including those with ToF, surgery is linked to a decrease in ventricular contractile function, most marked on the second post-operative day⁹³. A sub-group of patients with ToF have a significantly poorer post-operative course, linked to a restrictive cardiac physiology, requiring longer intensive care recovery with prolonged inotropic support⁹⁴.

These patients with RBBB might therefore benefit from targeted pacing resynchronisation, in both the acute and longer-term setting, provided optimal sites within the RV are identified. Since the outflow tract and free wall of the RV show latest activation in patients with repaired ToF⁵⁴ these sites should theoretically constitute targets for lead placement when delivering cardiac resynchronisation therapy (CRT). However, this has not been formally evaluated – preliminary evidence has raised the tantalising prospect of using “sub-pulmonary RV CRT” to improve RV performance and clinical endpoints in outpatient populations⁸⁹. This is likely to be of particular importance in the early post-operative period when RV demand increases under haemodynamic stress. Further, optimisation of atrioventricular delays also appears to be important⁹⁰. At present, relatively little is known about the electrical activation sequence, underlying mechanical dyssynchrony and subsequent potential benefits of CRT in this cohort.

This study therefore sought to define the electrical activation pattern of the RV in patients undergoing surgical pulmonary valve replacement using intra-operative mapping techniques and assess the haemodynamic and echocardiographic effects of targeted epicardial pacing to the site of latest activation.

5.2 Methods

Following local ethical approval, all adults with repaired ToF or early surgical intervention of congenital PS referred for surgical pulmonary valve replacement (PVR) during March 2010 to June 2011 were approached for inclusion to this study. All had significant pulmonary regurgitation, as defined by moderate to severe PR on cardiac magnetic resonance imaging (regurgitant fraction > 25%) with symptoms, severe RV dysfunction or dilatation, and/or impaired exercise capacity. Participants underwent surgical PVR at my Institution (The Heart Hospital, London) by one of two surgeons experienced with this anatomy. The surgical procedure has been described in the Appendices section.

5.2.1 Electroanatomic Mapping

Electroanatomic mapping was undertaken following completion of the surgical procedure, whilst the heart was still exposed. All patients had been rewarmed and were off cardiopulmonary bypass. All were haemodynamically stable, in sinus rhythm, and remained under general anaesthesia. The method for electroanatomic mapping has been described in the Materials & Methods section.

5.2.2 Acute haemodynamic study

Baseline and study measurements of cardiac parameters were derived using the Edwards Flotrac System as previously described.

Once a patient was clinically stable on the intensive care unit (normally within 3 hours of undergoing electroanatomic mapping) and whilst still fully sedated, pacing was undertaken. Atrial and ventricular epicardial pacing wires were connected as necessary so as to generate DDD RVA (apical), DDD RValt or DDD BiRV pacing. Pacing was performed in all three modes at two different atrioventricular delays (intrinsic PR -20ms; intrinsic PR -40ms) at 10% above the patients' own intrinsic heart rate. Each patient also underwent AAI pacing - to serve as a baseline with which to compare all other modalities. Each pacing burst was programmed for one minute and was followed by a return to intrinsic rhythm (no pacing) between bursts. Pacing order was determined using an online random sequence generator and all modes repeated three times to take into account normal physiologic changes that might occur during the study period. A total of 21 pacing bursts were therefore delivered, all in random order.

ECG recordings were taken at baseline and at each pacing mode for later analysis. These were scanned and analysed in the usual fashion.

5.2.3 Sub-acute echocardiographic study

A subset of patients underwent further echocardiographic evaluation during pacing three to four days post procedure. Images were obtained using a Vivid 7 (GE Vingmed, Milwaukee, Wis) by an operator experienced in scanning CHD patients (JO'L). Exactly the same randomised pacing protocol was performed as in theatre except more prolonged pacing was undertaken for two to three minutes to allow acquisition of the necessary images following a preceding, and full, baseline study. Each pacing mode was followed by a return to intrinsic rhythm (no pacing) between modes. Pacing order was determined using an online random sequence generator but only repeated once giving a total of seven pacing modes.

Echocardiographic images were imported and subsequently analysed offline by one experienced operator using a dedicated GE workstation (GE Vingmed, Milwaukee, Wis). Quantitative profiles (Q analysis software; GE Vingmed, Milwaukee, Wis) allowed for specific raw Dicom data to be analysed for any degree of interventricular dyssynchrony with Tissue Doppler Imaging, by determination of significant (greater than 65msec) difference between the LV septal/lateral walls and the RV lateral wall during peak strain. Global RV function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) as measured by M-mode echocardiography by the maximum displacement of the lateral tricuspid annulus. For LV function determination, a single four chamber method of disk equation was used for a measurement of LV global function.

5.2.4 Statistical analysis

Data are presented as mean \pm standard deviation or median (range) as necessary. Student's paired or unpaired t-test or repeated measures ANOVA were used to analyse the data where appropriate. Repeated measures ANOVA were followed by Fisher's PLSD post-hoc analysis, all t-tests with Bonferroni correction as necessary. A p value <0.05 was considered significant. Statistical analysis was performed using StatView statistical software (SAS Institute Inc, North Carolina, USA) and all graphs produced using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, USA).

5.3 Results

5.3.1 Patient characteristics

Sixteen adults were included in this study, 50% (n=8) had ToF; 63% (n=10) were female. All had significant PR with mean CMR regurgitant fraction of $47 \pm 10\%$. All were in sinus rhythm with RBBB

pattern on surface ECG. Clinical characteristics of the study cohort are shown in Table 2. Mean age was 32 ± 11 years; mean pre-procedure QRS duration 136 ± 26 ms, mean pre-operative RV end diastolic volume (RVEDV) 183 ± 76 ml/m². Ten (63%) of those included had undergone previous transannular patch (TAP) repair, seven at the time of original ToF repair.

	Total	ToF	Congenital PS	<i>p value</i>
Number n(%)	16	8(50)	8(50)	-/-
Female n(%)	10 (63)	5	5	-/-
Age at PVR	32 ± 11	30 ± 8	36 ± 14	0.34
Age at original repair	3.3 ± 2.3	4 ± 1	2 ± 3	0.14
TAP (at original repair) n(%)	10(63)	7	3	-/-
Pre-procedure QRS duration (ms)	136 ± 26	137 ± 26	120 ± 4	0.20
RVEDV (ml/m ²)	183 ± 76	166 ± 40	205 ± 81	0.26
RVESV (ml/m ²)	89 ± 47	80 ± 30	103 ± 65	0.43
RVEF (%)	51 ± 8	53 ± 7	49 ± 10	0.40
LVEF (%)	57 ± 10	53 ± 12	60 ± 9	0.27
PR RF (%)	47 ± 10	45 ± 10	50 ± 10	0.28

Table 2: Clinical characteristics of the study cohort. No factor was significantly different between the two anatomic substrates.

Electroanatomic mapping

Mapping was undertaken without adverse incident in all patients. In two participants (both with ToF), electrogram analysis was not possible at the RV anterior wall due to significant scarring. A highly significant difference in electrical activation times was found in the whole group ($p=0.0013$). Post hoc analysis identified the RV free wall as the area most likely to be subject to delay, and electrical activation here occurred, on average, 37ms after the earliest activation time. The RV outflow tract was also subject to activation delay; on average activation started 27ms after the earliest activation time. Figure 19 shows a basic colour map representation of activation across the RV in both ToF and congenital PS, with and without TAP repair.

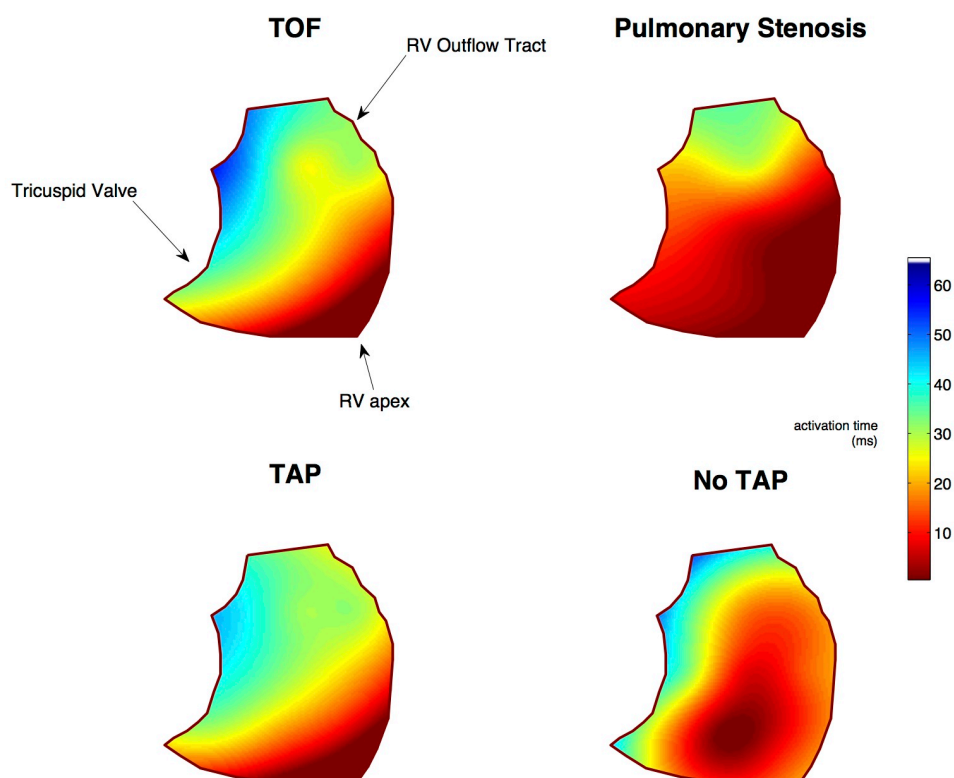


Figure 19: Basic activation maps of the RV surface for each anatomy studied. Although the RV free wall had the greatest delay in activation in whole cohort, the RVOT was subject to the greatest *variation* in activation, being latest in those with TAP repair and/or ToF.

Table 3 presents the activation delays at both these locations in the cohort as a whole, and per diagnosis. Interestingly, those with repaired ToF and those with previous TAP repair had significantly greater delay at the RVOT than those with either congenital PS or no TAP repair ($p=0.01$; $p=0.02$. Table 3, Figure 19). Those with TAP repair had greatest activation delay at the RVOT, though this did not reach statistical significance.

	Free wall	RVOT	p value
Total	37±33	27±25	-/-
ToF	48±31	41±17*	0.5
Cong PS	23±32	13±25*	0.4
TAP repair	37±23	39±16†	0.8
No TAP repair	25±37	6±25†	0.2

Table 3: Activation delay compared to earliest activation time (time 0). All times are in ms.

† $p=0.01$; * $p=0.02$

Acute post-operative pacing

All recruited patients were paced, and there were no pacing-related adverse events. Further, all patients were haemodynamically stable throughout recovery and none required formal temporary pacing during this time.

All modes of pacing, including AAI pacing, generated increases of CO, CI and SV significantly above baseline (Table 4). MAP did not change significantly with any mode of pacing ($p=0.49$). DDD RV alt pacing with AV delay minus 20ms of intrinsic was associated with the greatest overall increase in central haemodynamics (Table 4), and this significance was maintained when directly compared to DDD RV apical pacing at the same AV delay: CO (5.8 ± 1.3 to 6.4 ± 1.7 ; $p=0.018$), CI (3.4 ± 0.8 to 3.7 ± 1.0 ; $p=0.02$) and SV (63 ± 13 to 68 ± 17 ; $p=0.007$) (Figure 20).

	Baseline (intrinsic)	AAI	DDD RVA - 20ms	DDD RVA - 40ms	DDD RV alt - 20ms	DDD RV alt - 40ms	DDD BiRV - 20ms	DDD BiRV - 40ms	<i>p value</i> (ANOVA)
CO (L/min)	$4.7\pm1.2^\dagger$	5.5 ± 0.9	$5.8\pm1.3^*$	5.9 ± 1.3	$6.4\pm1.7^*$	6.1 ± 1.4	5.9 ± 1.5	5.9 ± 1.3	0.003
CI (L/min/m ²)	$2.7\pm0.7^\dagger$	3.2 ± 0.5	3.4 ± 0.8	3.5 ± 0.9	3.7 ± 1	3.6 ± 0.9	3.5 ± 0.9	3.5 ± 0.8	0.004
SV (ml)	$58\pm16^\dagger$	61 ± 10	63 ± 13	64 ± 13	68 ± 17	66 ± 14	65 ± 15	65 ± 13	0.01
MAP (mmHg)	$70\pm11^\dagger$	74 ± 10	72 ± 10	73 ± 9	72 ± 10	73 ± 10	74 ± 9	74 ± 10	0.49

*Direct paired t test $p=0.018$

† not included in repeated measures ANOVA

Table 4: All forms of pacing, including AAI pacing, generated increases of CO, CI and SV significantly above baseline however DDD RV alternate site pacing was found to generate the greatest increase in all measured parameters. MAP did not change significantly with any form of pacing ($p=0.49$).

5.3.3 QRS duration

Mean QRS duration for the whole cohort pre procedure was 136 ± 26 ms. Although a visible trend is seen, there was no significant difference in QRS duration between those with a diagnosis to ToF or congenital PS (137 ± 27 vs 120 ± 26 ; $p=0.20$) or those with and without a history of TAP repair (134 ± 23 vs 116 ± 8 ; $p=0.16$).

Both forms of RV apical pacing were associated with a significantly wider QRS duration than occurred during AAI pacing, though there was no significant difference in QRS duration when comparing the alternate pacing sites (RVA to RValt -20ms $p=0.11$; RVA to RValt -40ms $p=0.07$).

Figure 21 presents the mean data for each pacing programme. Full QRS data on two patients (one ToF, one PS) was not available.

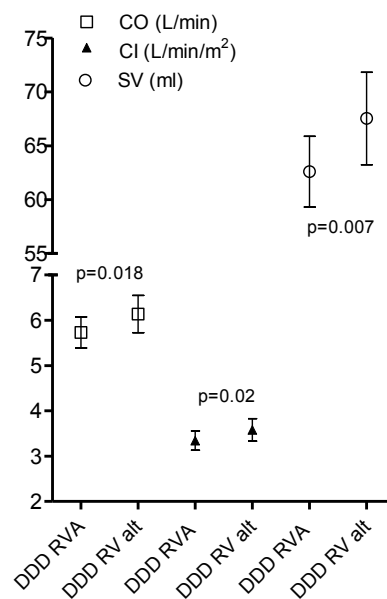


Figure 20: Direct comparison of DDD RV apical pacing with DDD RV alternate site pacing shows that the latter is associated with significantly increased haemodynamic variables. All AV delays at intrinsic minus 20ms.

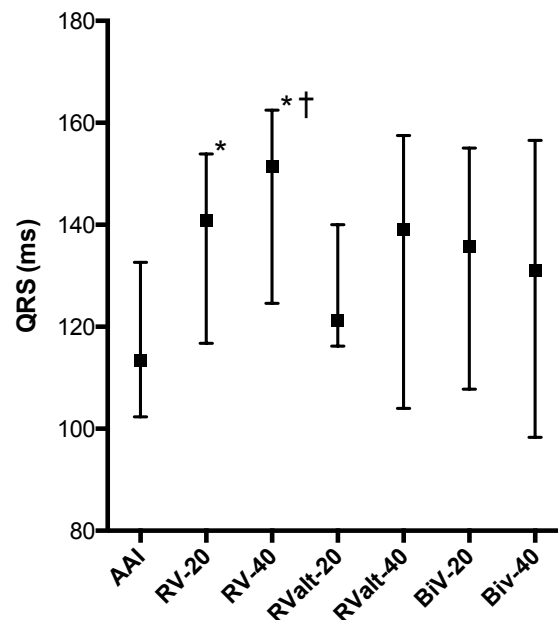


Figure 21: Mean QRS durations with each pacing mode and sinus rhythm (SR). RV apical pacing generated the widest complexes.

*denotes p=0.005 compared to AAI pacing.

5.3.4 Sub acute echocardiographic study

A subset of seven patients underwent echocardiographic study. Four opted not to take part in this second stage, one patient with ToF had unfortunately already had her pacing wires removed on the ward earlier, and in the remaining four electrical capture via one or more pacing wires was technically difficult, probably due to movement.

Of the seven patients, three had ToF and four had congenital PS. All patients with ToF had undergone TAP repair as had one additional PS patient. Five were female (71%). All had LV ejection fractions greater than 50% and none showed interventricular dyssynchrony prior to pacing, nor at any time with any modality of pacing.

Assessment of RV and LV contraction by both tissue Doppler analysis and M-mode echocardiography confirms that RV apical pacing at any AV delay is significantly worse than that measured at baseline – ie, with no pacing (Figure 22). No pacing mode was found to improve on baseline measurements.

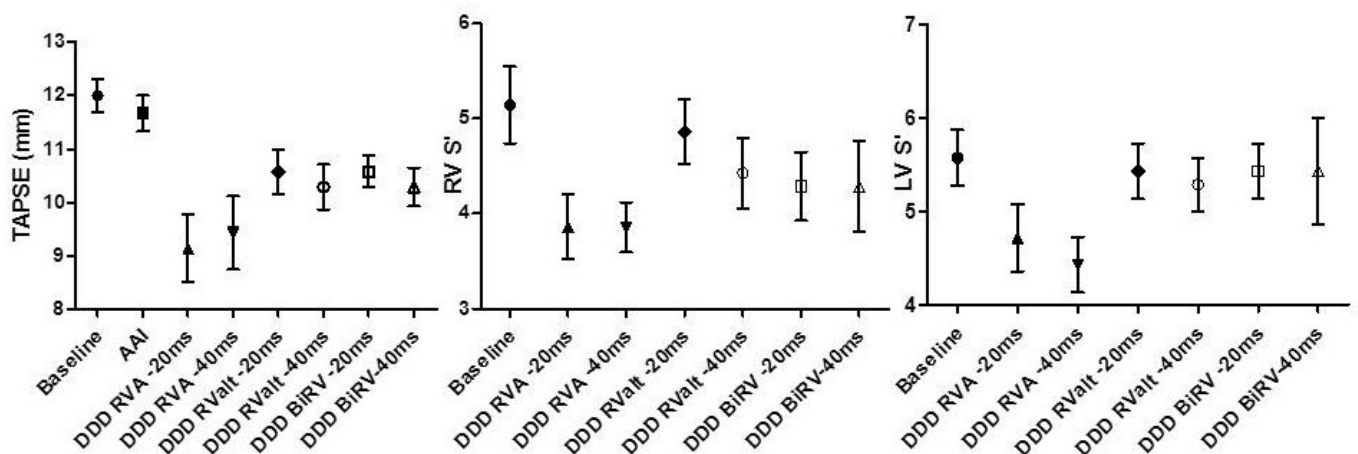


Figure 22: RV apical pacing was associated with deterioration of both RV and LV longitudinal contractility but no other form of pacing was found to be superior to no pacing.

5.4 Discussion

This is the largest study examining targeted single and dual site pacing in the RV of adults with repaired ToF or pulmonary stenosis. Electroanatomic mapping confirmed that whilst there is no uniform pattern to activation of the RV, the latest area of electrical activation in these adults is often the RV free wall; however, the RVOT is subject to the greatest variation in activation, being latest in those with TAP repair and/or ToF. This study confirms that targeted (alternate) single site RV pacing significantly improves cardiac haemodynamics acutely, more so than RV apical pacing or dual site RV

pacing. RV apical pacing either exerted a minimal or detrimental effect on haemodynamics and RV echocardiographic function.

5.4.1 Electrical activation of the right ventricle

Analogous to LBBB, RBBB is a complex electrical disease. Findings in this study of a lack of uniformity to activation across the cohort and are in keeping with the knowledge that block to the right bundle can occur at different levels, proximal, distal and terminal, depending on the location and extent of original (surgical) insult^{33,34,35}. Further, although all these levels of block manifest different electrical activation sequences on electrophysiological mapping, all are represented by a similar RBBB pattern on the surface ECG. When directly comparing, therefore, those patients who had a transannular patch repair with those that had not, it is perhaps unsurprising to note that the former had significant delays in electrical activation compared to the latter. Thus, although both the RV free wall and RV outflow tract had similar levels of activation delay in the whole cohort, the RV outflow tract was subject to the greatest variation, depending on anatomy and mechanism of original repair.

These results correspond to a high density epi- and endocardial mapping study of Falloot's patients which demonstrated that the RVOT and infundibular area was the latest site of activation in 73% of the 15 cases studied – indeed, the degree of delay between apex and RVOT was equivalent to the finding of approximately 50ms when the RVOT was the latest activating region¹⁸¹. Furthermore, significant LV epicardial activation delays were also identified, indicating that RBBB in ToF is linked to left ventricular electrical dyssynchrony. Importantly that study did not examine the effects of pacing on haemodynamics. However, in a limited combined body surface mapping and biventricular pacing study of ToF patients the infundibulum was found to be the latest site of activation and BiV (ie; RV-LV) pacing improved exercise capacity and dyssynchrony parameters¹⁸⁰. Interestingly targeted latest site RV pacing was not performed only conventional RV apical pacing and BiV stimulation.

This current study did not find the RV apex was subject to significant delay, in keeping with previously published studies^{54,181}. Further, the degree of RV volume overload and PR was similar in the whole cohort, as was LV function, suggesting that haemodynamic factors were not related to the electrical findings.

5.4.2 Resynchronisation pacing

Regardless of the underlying cause, the level of functional block and its consequent effect on local mechanical response are of paramount importance when considering the delivery, and thus efficacy,

of cardiac resynchronisation therapy. My study finds that targeted, alternate site, RV pacing leads to superior improvements in CO, CI and SV when compared to AAI pacing alone or DDD RV apical pacing in adults late after repair of ToF or congenital PS. I show that RV pacing alone does not confer significant advantages over AAI pacing, and in fact is associated with prolongation of the QRS duration and decrease in longitudinal contractility of the RV and LV. Interestingly, the combination of targeted alternate site RV pacing and RV apical pacing (DDD BiRV) does not lead to a further improvement in haemodynamics, and indeed also appears inferior to alternate site RV pacing alone.

This is the first study in this population to directly compare DDD RV apical pacing and best alternate site RV pacing. Although it supports the concept of 'sub-pulmonary RV CRT' in this cohort, long-term effects in terms of iatrogenic dyssynchrony need to be established. Thambo and colleagues reported that such therapy was associated with marked dyssynchrony of both the LV and the RV in a small cohort, though RV pacing sites were not directly targeted and dyssynchrony was most marked with RV apical pacing⁹². The fact that considerable epicardial conduction delays also affect the left ventricle in ToF has important implications for lead placement.

Although RV disease is predominant in this congenital population, it does not occur in isolation and the possibility of iatrogenic dyssynchrony in the long-term should be considered in the sub-aortic LV, especially if the systolic function of this chamber is already impaired. Abd El Rahman *et al* describe delayed activation of the LV in around half of patients with repaired ToF and RBBB⁵⁵. The pattern differed from that seen in patients with dilated cardiomyopathy and RBBB, affecting the ventricular septum and not the lateral LV wall. In a retrospective analysis of 75 patients with repaired ToF, Tzemos and co-workers noted a significant association between QRS duration and adverse LV volume, activation delay and septal strain⁵⁶, and recently, the Toronto group published their finding of significant delays in LV activation in their study group of adults with repaired ToF. It is already well established that RV apical pacing, both acutely and in the long term in the general population, is associated with LV dyssynchrony and functional impairment. My current findings indicate that such dyssynchrony as may be induced by additional RV apical pacing (ie with dual site RV pacing) may be sufficient to abrogate the benefits of targeted single site resynchronisation.

The acute nature of this study needs to be considered also: The phenomenon of ventricular interdependence explains how early surgical intervention on the RV and the subsequent effects of progressive haemodynamic lesions may negatively impact LV function by electromechanical uncoupling. A recent study looked at the degree of excursion of the intraventricular septum, the

main mediator of this phenomenon, in patients with repaired ToF. The group determined that in those with abnormal excursion there was a reduction in global and septal LV systolic function¹⁸². A study by Tobler *et al* determined that LV function improved in adults with ToF several years following surgical PVR, supporting the recovery of adverse electromechanical interactions between the two chambers⁵⁸. This finding has been documented elsewhere also¹⁸³; however, in both studies patients did better when there was already LV functional impairment. This was not the case in this current study.

5.4.3 Clinical Implications

Single site, targeted RV pacing led to significant improvements in global cardiac haemodynamics. In the acute setting, in those who suffer more protracted post operative courses linked to adverse RV function, targeted resynchronisation pacing would be of significant benefit in the immediate recovery period especially since it is clear that RV apical pacing is deleterious at worst, and at best neutral in effect. In terms of routine temporary pacing wire placement, these data indicate that epicardial RV leads should be placed in the outflow tract/free wall area of the RV as opposed to the apex.

5.4.4 Limitations

This was an acute study in a small population of patients. Invasive assessment of RV dP/dt may have provided more specific RV data acutely. Further, due to the early post-operative stage, echocardiographic imaging windows were not always optimal so assessment was sometimes limited. Echocardiographic assessment of the RV is more qualitative than cardiac magnetic resonance imaging (CMR) - the gold standard tool. However, several parameters of RV function, specifically TAPSE, have been shown to correlate well with RV ejection fraction as determined by CMR¹⁸⁴ and also corresponds to functional capacity. The complex interplay between changes in loading conditions and ventricular contractility associated with cardiac surgery dictates that haemodynamic measurements on day one may not be compared to non invasive measurements on day three post operatively. Longer term studies are necessary to determine the impact of alternate site pacing in a population of ToF patients with RBBB and RV impairment.

5.4.5 Conclusion

Single site RV pacing targeted to the region of latest intrinsic activation in patients with RBBB undergoing PVR induces acute improvements in central haemodynamics and supports the concept

of subpulmonary “RV CRT”. Targeted pacing in such patients has therapeutic potential both in the post-operative and chronic setting and is superior to RV apical pacing, which may be detrimental.

This Thesis has thus set out that electrical parameters can foretell risk in those with a subpulmonary RV. Strategies to alleviate and accommodate this risk are on-going, as highlighted in these last chapters. In those patients with a systemic (subaortic) RV however, very little is known regarding the association between surface ECG parameters and risk - this population experiences a high incidence of morbidity and mortality as a result of arrhythmia, HF and/or SCD^{4,5} - survival rates of 76% at 20 years have been reported¹³, with a mean age at death of 27 ± 7 years⁴. In my next chapter therefore, I chose to examine the association between surface ECG parameters and mortality in order to determine whether a relationship also existed in this high-risk group.

CHAPTER 6: Relationship between ECG parameters and mortality in adults with a systemic right ventricle

6.1 Introduction

In TGA palliated by atrial switch redirection (Mustard or Senning procedure), impairment of systemic RV function relates to long-term outcome¹⁶; however, no easily accessible or widely applicable clinical marker has been identified to quantify risk and predict outcome for this complex congenital cohort.

Early research in patients with a systemic RV has found that abnormalities on the surface ECG may be relevant^{104,104,105}; however, data is somewhat contradictory and span different age and palliation cohorts: Sun *et al* found that QT dispersion (QTd) was an independent risk factor for SCD, being significantly greater in this group than in those who survived; however, the study cohort comprised patients immediately post atrial switch repair to a maximum of five years follow up¹⁰⁶. Kammeraad and colleagues also studied children and younger adults post repair where the mean age of SCD or 'near miss' event was 12.3 years¹⁰⁷. They report no significant disparity between measured QRS duration, QTd or QTc intervals between their study and control groups. Both Gatzoulis *et al* and Schwerzmann and co workers examined adults. The former determined that whilst both QRS duration and QTd were significantly increased in adults with a history of ventricular tachyarrhythmia, only the latter was predictive of such late events¹⁰⁴. Schwerzmann *et al* reported that when QRS duration was >140ms there was a 10 fold increased risk for SCD or sustained VT compared to <140ms¹⁰⁵.

This study therefore sought to examine the relationship between surface ECG parameters and arrhythmia burden and outcome in adults with a systemic RV late after atrial redirection surgery for TGA.

6.2 Methods

6.2.1 Study population

Case notes for all adults (>18 years) with atrial redirection surgery for TGA under regular follow up since 2000 at the Heart Hospital (London) were reviewed. Those with good quality ECG obtained at

the time of most recent follow-up were included for analysis. 82 patients fulfilled criteria and were thus included in this study. ECG's were analysed as previously documented.

Patients were divided into 3 subgroups according to arrhythmic history as evidenced either on ECG/during admission or routine Holter monitor; those with no documented arrhythmias, those with prior supraventricular arrhythmias (SVT – symptomatic or >30 beats), and those with prior ventricular tachyarrhythmias (VT; sustained or non-sustained (≥ 4 beats)). The fourth group comprised deceased patients and those undergoing cardiac transplant, irrespective of arrhythmic history. For the purposes of this study only patients dying from cardiac causes (heart failure, sudden cardiac death) were included in the analysis. Mode of death was obtained from the case notes and/or death certificates, as necessary.

6.2.2 Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate whether each parameter followed a Gaussian distribution. Values are expressed as mean \pm standard deviation (SD), median (25-75th percentile values) or percentages, as appropriate. Univariate comparisons were performed by Student's t-test, Mann Whitney U test, and Chi-square test for normally distributed, non-normally distributed and categorical variables respectively. Pearson's or Spearman's correlation coefficients were used as appropriate to look for univariate associations between several continuous variables.

Cox proportional hazard analysis and receiver operator characteristic (ROC) curves were used to determine the relationship between QRS and QTc and mortality. Kaplan-Meier plots were generated from these results.

Differences were considered to be significant at a p value of <0.05 (two-tailed).

6.3 Results

There have been 15 (9%) TGA deaths at my Institution since the year 2000. Two were non cardiac (teratoma; primary hepatoma) and these were excluded from further analysis. The remainder comprised 5 SCD (33.3%) and 8 HF related deaths (53%) including one peri heart-lung transplantation. Excluding the non-cardiac modes of demise, mean age at death was 29 ± 10 years, median age at palliation was 36 months (range 0.5-144) and 62% (n=8) had undergone Senning procedure (Table 5).

Sixty nine patients (84%) are currently under continued follow-up at my Institution. Mean age of this cohort was 28 ± 6 years and median age at palliation 7 months (range 1-96). Thirty-two percent (n=21) were female, and 51% (n=35) had undergone Senning palliation (Table 5). Sixty-six percent (n=46) had no documented arrhythmias, 25% (n=17) had documented episodes of SVT, and 9% (n=7) had documented VT.

	Alive	Dead	p value
N	69	13	-/-
Age (yrs)	28 ± 6	29 ± 10	0.74
Age at palliation (mths)	7 (1-96)	36 (0.5-144)	<0.0001
Senning, n (%)	35 (51)	8 (62)	0.74
Female, n (%)	20 (32)	4 (31)	0.71
Length of follow-up (mths)	29 ± 1	9 ± 2	<0.0001
Devices, n (%)			
PPM	6 (9)	4 (27)	0.07
CRT	0	1 (8)	-/-
ICD	2 (3)	1 (8)	0.40
Medication, n (%)			
B blocker	14 (20)	2 (15)	0.65
ACEi/ARB	21 (30)	7 (47)	0.31
Diuretics	6 (9)	8 (53)	<0.0001

Table 5: Patient characteristics in each of the two major study groups.

Key: PPM permanent pacemaker, CRT cardiac resynchronisation device, ICD implantable cardioverter defibrillator, ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker

Of the total cohort (n=82) 71% had 'simple' TGA with the remainder (29%) having either required later surgical revision of the atrial pathways or having associated ventricular septal defect ('complex' TGA).

6.3.1 Arrhythmic type

Table 6 presents mean and median values as necessary for all measured ECG parameters within each of the subgroups. QRS duration increases significantly with changing arrhythmia malignancy and is greatest within the deceased subgroup ($p=0.0003$). QTc interval is also significantly different ($p=0.0009$). Of note, neither QRSd nor QTd show any significant changes within any of the arrhythmic subgroups (Table 6).

	No arrhythmias	Supraventricular	Ventricular	Deceased	P value†
<i>ECG parameters</i>	n=46	n=17	n=7	n=13	
QRS *(ms)	86 (79-96)	91 (80-103)	107 (87-153)	113 (104-142)	<0.0001
QRSd (ms)	30±10	37±13	34±11	34±7	0.168
QTc *(ms)	394 (318-405)	390 (382-443)	385 (373-454)	443 (410-465)	0.0006
QTd (ms)	51±17	58±25	59±12	60±13	0.31
JTd (ms)	48±14	53±15	64±17	59±19	0.016
<i>CMR imaging parameters</i>	n=30	n=9	n=5		
RVEDV (ml/m ²)	103±22	109±32	124±31	N/A	0.237
RVESV (ml/m ²)	48±17	54±32	68±25	N/A	0.181
RVEF (%)	54±9.	49±10	47±9	N/A	0.230
LVEF (%)	63±7	57±16	69±14	N/A	0.079
<i>Biochemical parameters</i>					
BNP * (pmol/L)	17 (11 to 28)	54 (25 to 121)	72 (26 to 98)	N/A	0.001

Table 6: RV -right ventricular, EDV end diastolic volume, ESV end systolic volume, EF ejection fraction, LV left ventricular, BNP NT-pro brain natriuretic peptide.

*denotes those values that are significant. † Values measured across 3 or 4 groups as available.

Outcome

Analysis of the study cohort as two independent groups – those alive at the time of investigation (n=69), and those deceased (n=13) – found that both QRS duration and QTc interval are significantly different: mean QRS duration 94ms vs 118ms and mean QTc interval 400ms vs 445ms in living and deceased patients respectively (p=0.002 for both; Figure 23). In univariate analysis both QRS duration and QTc interval were associated with increased risk of death (p<0.0001 for both): QRS hazard ratio 15 [95% confidence interval 3.3-68.6] and for QTc interval hazard ratio 10.7 [95% confidence interval 2.3-49]. A QRS duration cut off of >104ms had a sensitivity and specificity of 96% and 66% in predicting death whilst a QTc interval >406ms had a sensitivity and specificity of 96% and 56% for predicting death (Figure 24). Two year mortality was 36% when QRS duration < 104ms and 88% when >104ms (p<0.0001 for difference). Multivariate analysis was not possible due to the strength of association of these two factors. No marker of dispersion was associated with outcome when analysed independently.

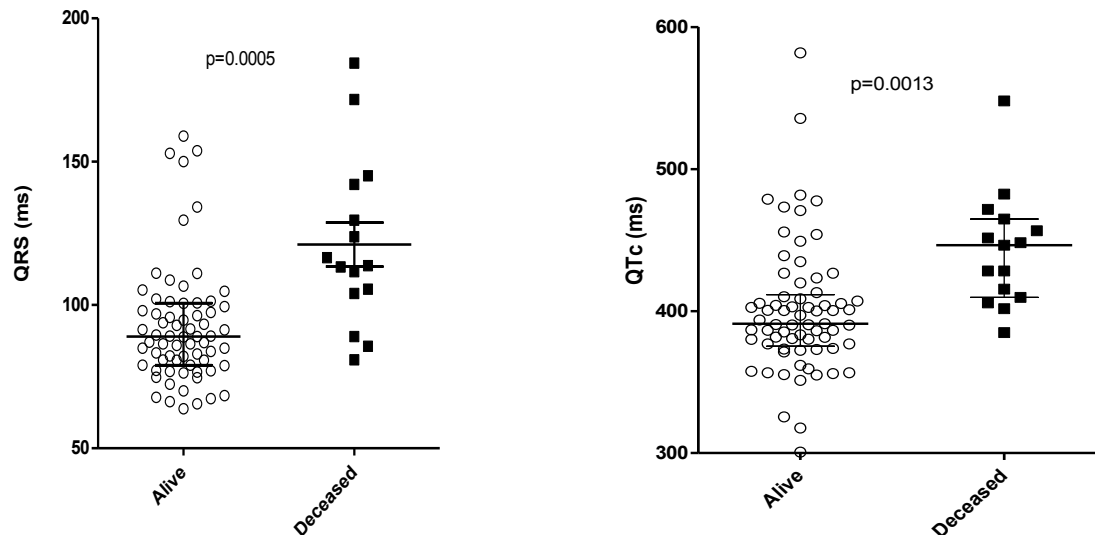


Figure 23: Comparison of values for QRS duration (left) and QTc interval (right) in the cohort remaining under follow up and those that have died during follow up finds significant differences.

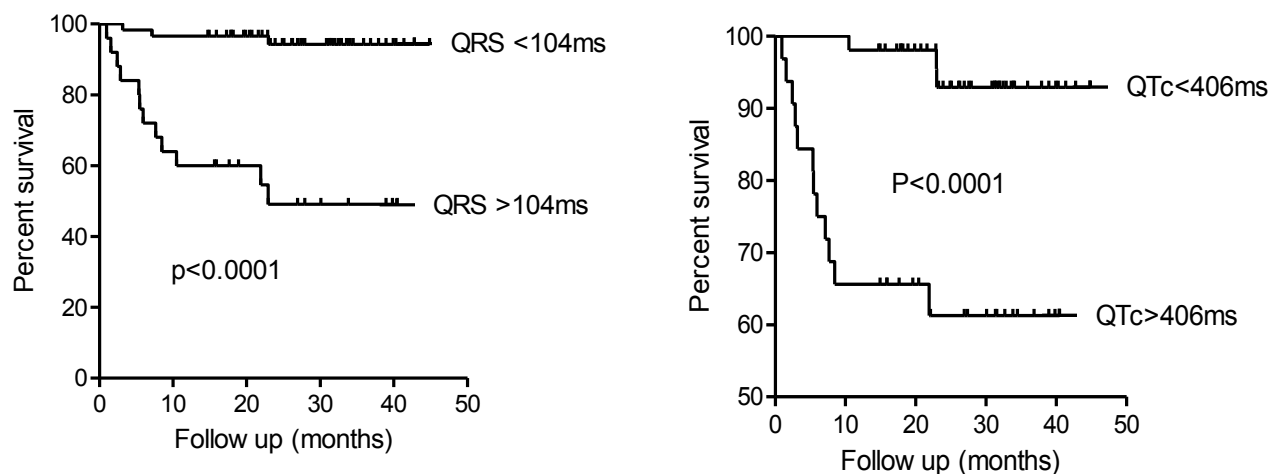


Figure 24: Kaplan Meier survival curves for QRS (left) and QTc (right): QRS>103ms has an OR 13.26 (CI 3.60 to 48.85, $p<0.001$) compared to QRS <103ms, and those with QTc>406ms have 13.27 (CI 2.97 to 59.36, $p=0.001$) greater odds of mortality compared to those below 406ms.

6.4 Discussion

This study finds that both QRS duration and QTc interval are independently associated with mortality in adults late after atrial switch redirection surgery for TGA. Further; cut-off values for these two parameters are within the perceived 'normal' range. I find no relationship between QTd and arrhythmia propensity; however, note significant prolongation of QRS duration with increasing arrhythmia malignancy.

Morbidity and mortality is prevalent in young adults with atrial switch TGA⁴. Systemic RV systolic function deteriorates with time from palliative surgery and this in turn is linked to risk of arrhythmia and outcome^{16,17,104}. Easily applied predictive risk markers are currently not available, though research in this area is growing. The establishment of ubiquitous markers predictive of outcome would be of immense value in this complex cohort of congenital patients.

The bulk of evidence purporting QRS duration and QTc interval as valuable risk and outcome parameters is found in adults with acquired or cardiomyopathic heart disease - prolongation of either variable prompts further investigation of possible underlying cause and/or instigation of prophylactic or therapeutic measures, including device therapy^{119, 185,186,187,188,189}.

Increasing evidence is being obtained to show a similar association between ECG parameters and outcome in those adults with CHD and a subpulmonary RV; however, the underlying electromechanical conditions cannot be translated to those patients with a systemic RV, and in this population, the evidence is less clear cut.

In adults with Mustard palliation of TGA, QRS duration has been noted to increase with follow-up¹⁶. Gatzoulis and colleagues reported that those with previous arrhythmia (SVT or VT) had a significantly longer duration of QRS than those without⁵¹; however, in this cohort QRS duration did not relate to outcome. Kammeraad and co-workers studied patients palliated by Mustard and Senning techniques and found no significant differences in QRS duration when comparing patients who had suffered sudden death with those that had not¹⁰⁷. This cohort constituted younger patients however, whereas Schwerzmann *et al* determined that a QRS duration >140ms was associated with risk of malignant arrhythmia and sudden death adults with Mustard repair¹⁰⁵.

QTc interval has been the subject of less investigation: Roos-Hesselink did document that this did not increase with follow-up¹⁶. Kammeraad *et al* found no significant difference in QTc interval when comparing sudden death events with a matched cohort¹⁰⁷.

6.4.1 Implications

The finding of relatively narrow measures for both QRS duration and QTc interval in relation to risk and outcome will demand regular scrutiny of the 12 lead ECG in this population. If identified, such patients should be regarded as 'high risk' and subsequent investigations undertaken as necessary to help further delineate this risk. Anti-heart failure medications should be considered as required;

however, in the absence of clear compromising haemodynamic lesions or other reversible cause, this study would suggest a low threshold for consideration of prophylactic implantable cardioverter-defibrillator insertion.

The establishment of a QRS duration >104ms as being independently linked with risk of death demands reconsideration of 'normal' definitions in a population of patients who, by necessity, are subject to lifelong abnormal cardiac physiology⁹⁹. My findings carry implications for cardiac resynchronisation therapy given the increased risk at such a 'narrow' QRS duration. Further, the question of earlier, unseen, compromise to RV systolic function reflected by this increased risk, with long-term bradyarrhythmia pacing also merits consideration.

6.4.2 Conclusion

QRS duration >104ms and/or QTc interval >406ms are related to increased risk of death in adults late after atrial redirection surgery for TGA. I propose that serial monitoring of the surface ECG for these parameters form a routine assessment in all patients with atrial redirection surgery for TGA. In association with proven or clinical suspicion of arrhythmia, a QRS duration >104ms and/or QTc interval >406ms should prompt full investigation and consideration, as necessary, of early initiation of antifailure and/or anti arrhythmia therapies.

This chapter therefore supports the theory that electrical parameters can be linked to outcome in those with a systemic RV, as they are known to be in those with a subpulmonary RV. In this latter group, electrical remodelling, either positive or negative, is associated with haemodynamic remodelling. There is a paucity of data examining any similar relationship between RV volumes and function and electrical parameters in the systemic RV and my next Chapter will therefore study this in closer detail. I have also chosen to include study of the neurohormonal biomarker NT-proBNP in this cohort of patients, examining its relationship in this complex congenital population to both RV volumes and function as determined by CMR and ECG measurements.

CHAPTER 7: Relationship of systemic right ventricular function to ECG parameters and NT-proBNP levels in adults with transposition of the great arteries late after Senning or Mustard surgery

7.1 Introduction

Outcome in the population of young adults with atrial switch palliation of TGA is related to the function of the systemic RV¹⁹⁰. Cardiac magnetic resonance (CMR) imaging is the most accurate and reproducible tool for assessing this^{112,113}; however, this method is time consuming and availability often restricted to specialist centres. The high prevalence of implanted pacing/defibrillator devices in this population and the small but significant proportion of patients with claustrophobia also limit its use. CMR imaging may be prompted following clinical assessment, yet patients notoriously under report functional ability and symptoms despite marked impairment on objective testing¹⁹¹. Cost effective and more readily available surrogate clinical markers that closely relate to ventricular function would therefore be highly desirable.

Elevated circulating brain natriuretic peptide (BNP) levels help identify patients with impaired systemic ventricular function⁹⁶ and relate to outcome in those with acquired heart disease¹⁹². In mixed cohorts of patients with congenital cardiac disease, BNP has been shown to relate to systemic ventricular function as determined by echocardiography¹⁴⁷ and to function of the pressure overloaded systemic and sub-pulmonary RV as determined by CMR¹⁴⁸. Surface ECG measures, including QRS width, have also been found to relate to RV size and function in the setting of pressure overload³⁶. The inter-relationship of systemic RV size and function with circulating BNP levels and surface ECG measures in adults with transposition of the great arteries late after atrial switch repair is unknown.

7.1 Methods

7.1.1 Study population

Data was routinely collected prospectively from consecutive adults with previous Senning or Mustard surgery for TGA attending a dedicated CHD heart failure clinic at my Institution between January 2008 and March 2009. Some of these patients had been included for study in the previous Chapter, however all current patients had undergone assessment of symptoms by NYHA functional

class, measurement of circulating N-terminal pro Brain Natriuretic Peptide (NT-proBNP) levels and surface ECG as part of their routine clinic work-up. CMR imaging was performed within 3 months of clinic attendance in accordance with clinic protocols.

7.1.2 Electrocardiography

Standard original hard copies were scanned and analysed as previously explained. ECG's were analysed by one observer (CP) who was blinded to NT-proBNP and CMR findings. Average QRS duration, QTc, QRS, QT and JT dispersions (d) were determined across the 12 leads as described in the Materials & Methods section.

7.1.3 NT-pro Brain Natriuretic Peptide

Peripheral venous blood was collected from each patient after they had rested for a minimum of 20 minutes. Samples were centrifuged and immediately analysed via sandwich immunoassay using electrochemiluminescence (E 170 Module, Roche Diagnostics, Basel, Switzerland).

7.1.4 Cardiac Magnetic Resonance Imaging

CMR imaging was performed using a 1.5T scanner (Avanto, Siemens Medical Systems, Erlangen, Germany), with assessment of ventricular volumes as previously described. Manual segmentation of the ventricles with exclusion of the major RV trabeculae from the blood pool volume was undertaken. Quantification of aortic forward flow volume using phase contrast volumetry provided an internal quantitative guide to the RV stroke volume and improves the accuracy of volumetric quantification in the presence of tricuspid valve regurgitation¹⁹³. Volumes were indexed to body surface area.

7.1.5 Statistical Analysis

The Kolmogorov-Smirnov test was used to confirm or exclude normal distribution for each variable. Values are expressed as mean \pm standard deviation (SD), median (25-75th percentile values) or percentages, as appropriate. Univariate comparisons were performed by Student's t-test, Mann Whitney U test, and Chi-square test for normally distributed, non-normally distributed and categorical variables respectively. Pearson's or Spearman's correlation coefficients were used as appropriate to look for univariate associations between continuous variables (SPSS Inc., Chicago, USA and GraphPad Software Inc, La Jolla, USA). Differences were considered to be significant at a *P* value of <0.05 .

7.3 Results

7.3.1 Patient characteristics

Thirty-five adults were included in the study. None suffered decompensated heart failure or compromising arrhythmia between time of clinic attendance and CMR imaging. Mean age was 29 ± 6.5 years at the time of clinic attendance and 14 ± 13.6 months at the time of surgery (54% a Mustard operation). Five (14%) patients had associated ventricular septal defects repaired at original palliation – ‘complex’ anatomy. Seven further patients (20%) underwent later surgical revision of atrial pathways. For the purpose of statistical analysis these 12 patients comprised the ‘complex surgical’ group. The remaining 23 patients had simple TGA and single stage surgery. Ten patients were taking beta-blockers (29%), 18 angiotensin converting enzyme inhibitors/angiotensin receptor blockers (51%), and 2 were on diuretic therapy (6%). Table 7 summarises baseline measurements of all investigations.

Twelve patients were in NYHA class II (34%) with the remainder in functional class I. Patients in NYHA class II had significantly longer QRS duration (90 ± 3 vs 113 ± 8 ms; $p=0.003$), QRSd (30 ± 2 vs 39 ± 4 ms $p=0.03$) and QTc interval (390 ± 8 vs 426 ± 17 ms; $P=0.03$) compared to those in functional class I. RV end systolic indexed volume (RVESVI) (48 ± 3 vs 64 ± 8 ml/m²; $P=0.04$) and NT-proBNP (29 ± 6 vs 56 ± 10 pmol/L; $p=0.02$) were also higher in patients in NYHA class II. There was no statistical difference between functional classes with respect to palliation method, age at follow-up, age at repair or RVEF.

7.3.2 Complex vs Simple Surgical Course

Compared to those with uncomplicated surgery, patients with complex anatomical and surgical history had higher NT-proBNP levels (55 ± 26 vs 20 ± 35 pmol/L; $P=0.002$) and longer QRS duration (116 ± 28 ms vs 89 ± 11 ms; $P=0.0004$; Table 7) whilst showing no difference in NYHA class, RV volumes or RV function. Four of those with ‘complex’ history had undergone Senning palliation as compared to 8 who had undergone Mustard palliation.

	All (n=35)	Surgery type		P value	Surgical intervention		P value
		Mustard (n=19)	Senning (n=16)		Simple (n=23)	Complex [§] (n=12)	
Age, median (range), years	29 (18-40)	33 (22-40)	25 (18-39)	0.0003	28 (18-38)	34 (19-40)	0.17
Age at surgery, median (range), months	9 (1-52)	12 (3-52)	6 (1-48)	0.01	9 (4-36)	13 (1-52)	0.02
Male/female	24/11	11/8	13/3	---	15/8	9/3	---
NYHA functional class I/II	23/12	11/8	12/4	---	18/5	6/6	---
CMR							
RVEDVI, mL/m ²	107±27	111±25	104±30	0.47	103±24	117±32	0.16
RVESVI, mL/m ²	53±21	55±23	50±19	0.44	50±7	60±31	0.16
RVEF, %	51±8	50±8	52±8	0.65	52±7	49±10	0.25
NT-proBNP, pmol/L	26 (5-135)	31 (17-135)	12 (5-73)	0.01*	20±35	55±26	0.002
ECG							
QRS, ms	98±22	101±23	94±21	0.36	89±11	116±28	0.0004
QTc, ms	402±47	414±57	388±26	0.10	395±39	420±59	0.15

Table 7. Patient characteristics and results for Cardiac Magnetic Resonance, NT-pro BNP and ECG measures in all patients and according to surgical history. Values are mean±SD unless stated otherwise. RVEDVI and RVESVI refer to indexed right ventricular volumes during diastole and systole respectively. Definitions of simple and complex surgical course are given in the text. *P value becomes NS when corrected for age. [§]Encompasses those with complex anatomy and those with further surgical reintervention.

7.3.3 Cardiac Magnetic Resonance Imaging

For the cohort as a whole, mean RV end diastolic indexed volume (RVEDVI) was 108±27ml/m², mean RVESVI 53±21ml/m² and mean RVEF 51±8%. RVEDVI did not relate to age at follow up ($P=0.8$) or age at palliative surgery ($P=0.5$). There was also no statistical difference when comparing CMR measures between those with Mustard and Senning palliation.

7.3.4 NT-proBNP measurements

Mean plasma NT-proBNP concentration was 38±34 pmol/L. There was no relationship between NT-proBNP and age at clinic attendance or age at palliation. There was a trend towards higher NT-proBNP levels in females ($p=0.054$) but values were unrelated to renal function (creatinine $p=0.6$). NT-proBNP levels were significantly higher in those with Mustard palliation compared to those who underwent Senning surgery (50±38 vs 23±22; $p=0.01$), but this significance was lost when adjusting for age ($p=0.09$).

NT-proBNP and CMR

There was a significant negative correlation between NT-proBNP levels and RV ejection fraction ($r = -0.54$, $p=0.0007$; Figure 25) corresponding with significant positive correlations between NT-proBNP

levels and both indexed end diastolic and systolic volumes ($r=0.43$, $p=0.01$ and $r=0.53$, $p=0.001$ respectively; Table 8). No association was found between NT-proBNP levels and LV ejection fraction or LV volume measurements.

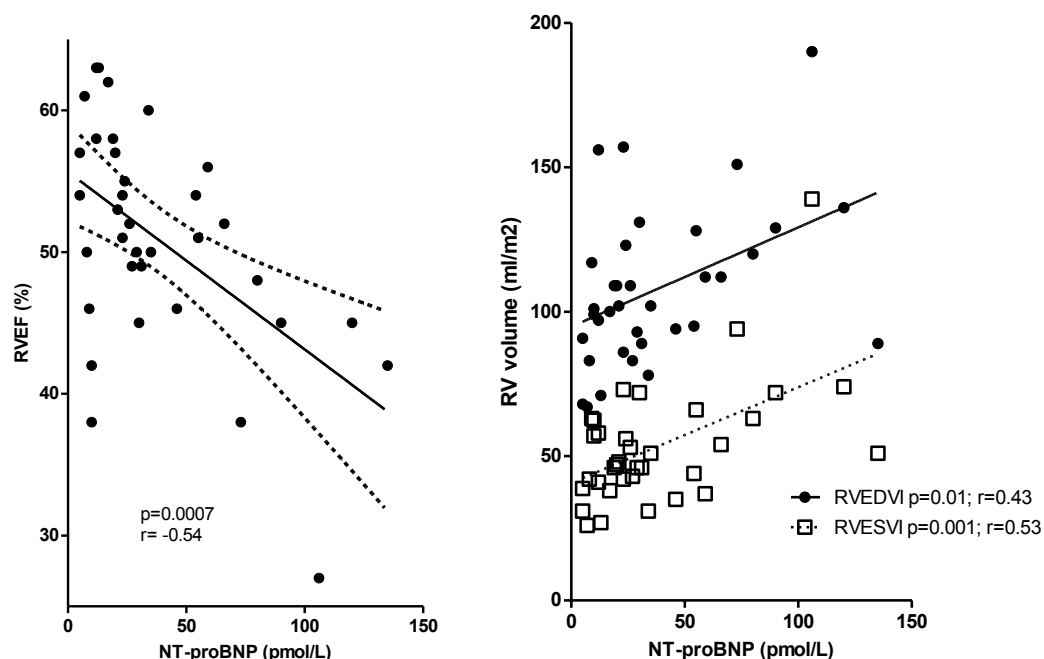


Figure 25: Correlations between right ventricular ejection fraction (panel a), or indexed right ventricular volumes (panel b), and NT-proBNP.

	RVEDVI	RVESVI	RVEF
NT-proBNP	$r=0.43$ $p=0.01$	$r=0.53$ $p=0.001$	$r=-0.54$ $p=0.0007$
QRS	$r=0.47$ $p=0.0004$	$r=0.53$ $p=0.001$	$r=0.37$ $p=0.03$
QRSd	$r=0.60$ $p=0.0001$	$r=0.63$ $p<0.0001$	$r=0.37$ $p=0.03$
QTc	$r=0.41$ $p=0.016$	$r=0.45$ $p=0.007$	$r=0.39$ $p=0.02$
QTd	$r=0.46$ $p=0.005$	$r=0.50$ $p=0.002$	$r=-0.20$ $p=0.29$

Table 8: Correlation coefficients of Cardiac Magnetic Resonance measurements with NT-proBNP and ECG parameters. RVEDVI and RVESVI refer to indexed right ventricular volumes during diastole and systole respectively.

7.3.5 ECG measurements

Mean QRS duration was 98 ± 23 ms, QTc interval 402 ± 47 ms, QRSd 33 ± 12 ms, JTd 53 ± 18 ms and QTd 57 ± 22 ms. No ECG parameter related to age at follow-up, age at palliation or the palliative subtypes.

ECG and CMR

QRS duration, QRSd, QTc and QTd all correlated significantly with both RVEDVI and RVESVI (Table 8), the most significant correlation being between QRSd and RVEDVI ($r=0.60$, $P\leq 0.0001$; Figure 26). QRS duration, QRSd and QTc all had inverse relationships to RVEF. Only QTd showed no relation with RVEF and it was the only ECG parameter to show a correlation with LVEF ($r= -0.39$, $P=0.02$).

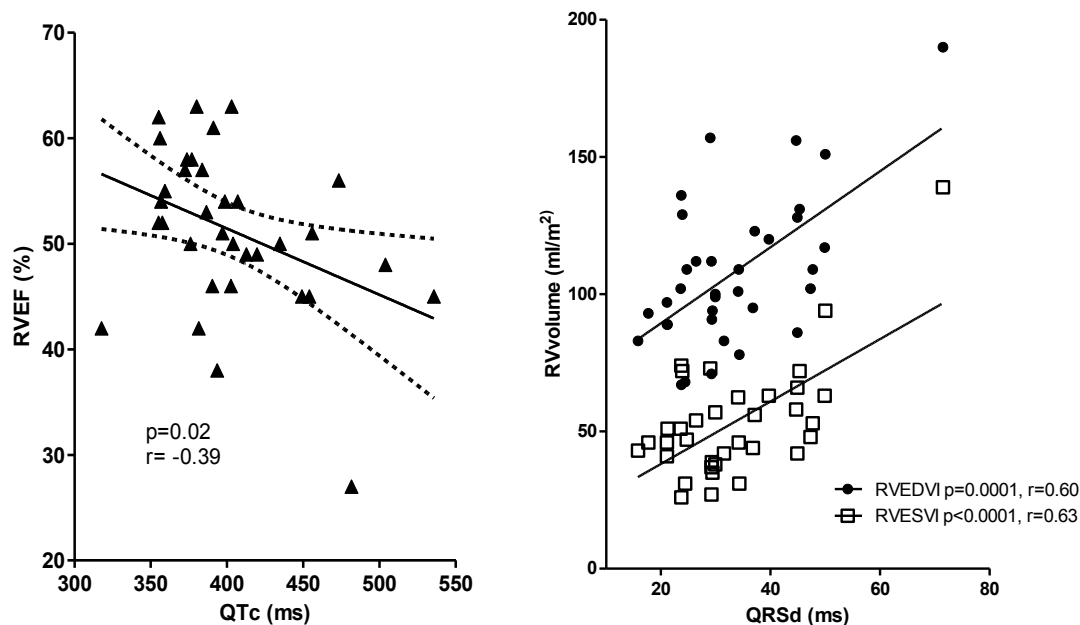


Figure 26: Correlations between right ventricular ejection fraction and QTc (panel a), and indexed right ventricular volumes and QRS dispersion (panel b).

7.4 Discussion

This is the largest prospective study examining the inter-relationship between NT-proBNP, ECG parameters and systemic RV function in a homogenous cohort of adults late after atrial switch redirection surgery for TGA. It demonstrates that larger systemic RV volumes and lower ejection fractions are associated with higher circulating levels of NT-proBNP and longer ECG measures of ventricular depolarisation and repolarisation. This pattern of falling systemic ventricular function, increasing circulating natriuretic peptide levels and prolongation of ECG measures characterises the heart failure syndrome in acquired heart disease and adds further support to the view that many congenital heart diseases are, in essence, heart failure syndromes⁹⁹.

It is interesting to note that NT-proBNP levels were higher and QRS width longer in the group with complex anatomical and surgical history compared to those without, whilst at the same time NYHA class and CMR measures of RV volumes and function showed no difference between these groups.

These findings suggest that NT-proBNP levels and ECG parameters provide information about heart failure status over and above that determined by symptom assessment and CMR.

The subjective nature of symptom scores and the poor correlation between symptoms and cardiopulmonary exercise capacity, a powerful predictor of prognosis¹⁹¹, is well known. The relatively poor prognostic power of left ventricular ejection fraction in patients with acquired heart failure compared to ventilatory efficiency and natriuretic peptide levels is also well documented¹⁹⁴. Taken together with these findings, this suggests that symptom assessment and measurement of RV volumes and function alone may not provide the optimum description of pathological processes in a particular patient and may not be the best measures to use when determining future risk. It would be helpful to clarify the relative prognostic power of these various measures in futures studies.

7.4.1 Natriuretic peptides and systemic right ventricular function

NT-proBNP levels were higher in the Mustard cohort compared to the Senning cohort. This perhaps reflects developing surgical practice, with earlier age at palliation using the Senning technique superseding the relatively later palliation age with the former technique. The trend towards significantly higher levels after adjusting for these variables; however, implies that an intrinsic disadvantage of Mustard surgery over the Senning operation cannot be excluded with confidence on these data.

NT-proBNP levels correlated significantly with RVEDVi and RVESVi. BNP levels have also been shown by others to relate to the severity of tricuspid regurgitation and RV volume overload following Mustard and Senning surgery^{146,195}. Tulevski and colleagues included 9 patients with TGA palliated by Mustard or Senning procedure in a heterogenous group and found that RVEF, measured by CMR, correlated negatively to BNP levels ($r = -0.65$)¹⁴⁸. Garg and co-workers found no correlation between RVEF and BNP in patients with systemic RV physiology, although there was a strong correlation with atrial natriuretic peptide (ANP)¹⁵³; a somewhat surprising result as both ANP and BNP correlate exceptionally closely ($r = 0.91$, $P < 0.0001$) in adults with CHD¹⁴⁷.

Although similar relationships between BNP levels and RV volumes have also been described in the context of sub-pulmonary RV anatomy¹⁹⁶ Neffke *et al* found only a weak correlation between BNP and RVEDV³⁶ in a heterogeneous cohort with systemic or subpulmonary RV physiology. This suggests that pathophysiological responses differ between various anatomic substrates, reflected in the

mechanism of neurohormone production, and that these substrates might be better investigated in isolation.

7.4.2 Electrocardiographic markers and systemic right ventricular function

In patients with acquired heart disease, QRS duration is a measure of myocardial electromechanical dissociation, helps guide the prescription of resynchronisation therapy and is useful in assessing the risk of malignant arrhythmias⁹⁸. Prolongation of QRS duration and dispersion are likely to reflect the effects of chronic pressure overload and myocardial stretch on the systemic RV and indicate electromechanical uncoupling here also. This study demonstrates the close relationship between measures of ventricular depolarisation and repolarisation with volume and function of the systemic RV and indeed, Gatzoulis and colleagues reported similar associations with respect to QRS duration in a comparable cohort¹⁰⁴. Neffke *et al* found that QRS dispersion manifested a greater rate of change over time than QRS duration in this context³⁶, describing that the latter measure did not significantly increase over 5 years follow-up. This is in contrast to Roos-Hesselink and colleagues who confirm significant increases in QRS duration over long-term follow up in a large cohort accompanying deterioration in systemic RV function as measured by echocardiography

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Prolonged QTd has been shown to be an independent predictor of late arrhythmia in patients with Mustard palliation and, in combination with loss of sinus rhythm on the surface ECG, it has been associated with sudden cardiac death in adults with either Mustard or Senning palliation¹⁰⁶.

Recently, Schwerzmann and colleagues suggested that a cut-off QRS duration of >140ms defines a group of adults after Mustard palliation at increased risk of malignant arrhythmia or sudden death¹⁰⁵. By contrast, Kammeraad and co-workers were unable to find differences in QRS duration, QTc or QTd between patients with TGA that had died suddenly and those that had not¹⁰⁷.

The relationships of these various ECG parameters to electromechanical dyssynchrony in the systemic RV and to prognosis in palliated TGA therefore need further clarification. They may yet provide useful insight into the mechanisms that drive outcome and could help guide resynchronisation therapy in a group where the evidence base for this therapy remains narrow.

7.4.3 Limitations

Although this cohort represents a large sample size in this congenital population, these patients were only investigated at a single time point. Serial investigation will provide more data with

regards to prognostic value of NT-proBNP. Furthermore, and as previously stated, NT-proBNP measurements were undertaken within three months of CMR imaging, and are thus not concurrent. However, no patient suffered symptomatic decline necessitating admission in the interim.

7.4.4 Conclusion

This study of patients late after surgical palliation of TGA describes the close relationships between NT-proBNP, ECG parameters and measures of systemic RV function. Circulating peptide levels and surface ECG parameters constitute safe, cost effective and widely available surrogate markers of systemic RV function and provide useful additional information on heart failure status. Both measures hold promise as prognostic markers and their association with long-term outcome should be determined.

The next Chapter sought to further study the role of CMR imaging in evaluating the systemic RV. Diffuse fibrosis has been described in adults with LV disease and, in combination with neurohormonal markers, is considered a marker of cardiac disease severity. It's presence, and relation to other disease parameters in the systemic RV has not previously been investigated.

CHAPTER 8: Diffuse Myocardial Fibrosis in the systemic right ventricle of adults late after Senning or Mustard surgery

8.1 Introduction

As previously stated, though intra-atrial repair (Mustard and Senning operations) of TGA has been largely superseded by the arterial switch operation, there remains a sizeable population of adults under regular follow-up who underwent such early palliative surgery. With the morphologic RV supporting the systemic circulation, there is a high burden of early morbidity and mortality from heart failure and sudden cardiac death⁵. Long-term outcome in this cohort relates to the function of the systemic RV **Error! Bookmark not defined.** and CMR imaging is widely regarded as the best available imaging modality for this purpose^{112,112}.

Other markers of heart failure severity, including high circulating brain natriuretic peptide (NT-proBNP) levels and impaired cardiopulmonary exercise (CPEX) performance, have also been described in adults with CHD^{96,147,147}. Both measures have been shown to relate to long-term prognosis in mixed cohorts with CHD and in those with a systemic RV^{158,158,159,160,197,198}.

Myocardial fibrosis is considered to be a marker of disease severity and its presence is used to monitor disease progression and regression¹⁹⁹. In those with previous Mustard or Senning surgery, focal fibrosis, assessed using the late gadolinium enhancement (LGE) technique, has been found to correlate with systolic function of the systemic RV and with documented arrhythmia²⁰⁰. However, the LGE method does not allow evaluation of diffuse fibrosis and this latter has been found to correlate with systemic RV end-diastolic volume and ejection fraction in a small cohort described by Broberg *et al*²⁰¹. Equilibrium contrast CMR (EQ-CMR) has previously been validated against cardiac biopsy determination of diffuse fibrosis for assessment of left ventricular interstitial expansion (a surrogate marker of diffuse fibrosis in most disease states) in patients with severe aortic stenosis and hypertrophic cardiomyopathy²⁰². The technique is similar to that of Broberg, but the use of equilibrium contrast removes uncertainties regarding contrast kinetics in heart failure or renal impairment and does not require an assumption of pseudoequilibrium.

In this prospective study EQ-CMR was used to evaluate diffuse fibrosis in adults late after atrial redirection surgery for TGA, comparing the results to both normal subjects and also other heart failure parameters to determine its usefulness as a measure of disease severity.

8.2 Methods:

8.2.1 Study population

Fourteen adult patients with previous Senning or Mustard surgery for TGA, followed up in a dedicated CHD heart failure clinic at my Institution, were thus prospectively recruited between June 2009 and June 2010. These patients were of similar characteristics to their peers in the previous studies, but all patients underwent measurement of NT-pro BNP, CPEX testing and CMR imaging within a three-month period. This was a prospective study. None required admission for decompensated heart failure during this time. These patients were compared to 14 age and gender-matched normal subjects, as there is some evidence to suggest an increase in ECV with age²⁰³. All normal subjects underwent cardiac history and examination, 12 lead ECG and CMR to ensure they did not have any underlying cardiovascular disease. The study had Institutional approval and all patients and normal subjects gave informed consent to participate in the study.

8.2.2 NT-pro brain natriuretic peptide

Peripheral venous blood was collected from each patient after they had rested for a minimum of 20 minutes. Samples were centrifuged and immediately analysed via sandwich immunoassay, using electrochemiluminescence (E 170 Module, Roche Diagnostics, Basel, Switzerland).

8.2.3 CMR

CMR was performed using a 1.5T Siemens Avanto scanner (Siemens Medical Systems, Erlangen, Germany), with assessment of ventricular volumes as previously described. Manual segmentation of the ventricles, with exclusion of the major RV trabeculae from the blood pool volume, was undertaken. Quantification of aortic forward flow volume, using phase contrast volumetry, provided an internal quantitative guide to the RV stroke volume and improved the accuracy of volumetric quantification in the presence of tricuspid valve regurgitation¹⁹³. Volumes were indexed to body surface area.

Equilibrium contrast CMR

EQ-CMR, as previously validated against histology in aortic stenosis and hypertrophic cardiomyopathy²⁰², is an add-on to a standard clinical scan. We quantified the tissue volume of distribution, a marker of the extracellular volume (ECV), of the routine clinical contrast agent, Gadoteratemeglumine, (gadolinium-DOTA, marketed as Dotarem © Guerbet S.A. France) which partitions freely between the plasma and interstitial space but does not enter cells. Interstitial tissue volume is primarily determined by the amount of extracellular matrix. EQ-CMR involves three steps: 1) a standard gadolinium bolus followed by constant infusion to eliminate contrast kinetic effects and achieve an equilibrium contrast state throughout the body; 2) signal intensity (T1) measurement pre- and post-contrast equilibrium using CMR; and 3) a direct measure of blood volume of contrast distribution, by taking a complete blood count, and equating the blood volume of contrast distribution to one minus the haematocrit. The ECV is then calculated as²⁰⁴:

$$ECV = (1 - \text{hematocrit}) \times \frac{(1/T_{1 \text{ myocardium post contrast}} - 1/T_{1 \text{ myocardium pre contrast}})}{(1/T_{1 \text{ blood post contrast}} - 1/T_{1 \text{ blood pre contrast}})}$$

In this study, T1 mapping was performed using the same method as previously described, fast low angle single shot inversion recovery (FLASH IR) at increasing inversion times, in a mid-short axis slice.¹⁷ The blood T1 was assessed using a region of interest within the LV cavity. The myocardial T1 was assessed using a region of interest within the interventricular septum and also within the RV free wall.

8.2.4 Cardiopulmonary exercise testing

CPEX was performed on an electronically braked ergometer cycle (Lode, Groningen, Holland) with computerised breath-by-breath ventilator gas analysis (MedGraphics, Minnesota, USA). The CPEX protocol has been described in the Materials & Methods section.

8.2.5 Statistical Analysis

The Kolmogorov-Smirnov test was used to assess normality. Values are expressed as mean \pm standard deviation (SD), median (25-75th percentile values) or percentages, as appropriate. Univariate comparisons were performed by Student's t-test, Mann Whitney U test, and Chi-square test for normally distributed, non-normally distributed and categorical variables respectively. Pearson's or Spearman's correlation coefficients were used as appropriate to look for univariate

associations between continuous variables (SPSS Inc., Chicago, USA and GraphPad Software Inc, La Jolla, USA). Differences were considered to be significant at a *P* value of <0.05.

8.3 Results

8.3.1 Patient and control subject characteristics

The fourteen patients (6 female) had a mean age of 33.7 ± 6.5 years and median age at palliation of 9.7(7-20) months (Table 9). Six (43%) had Senning palliation. Details of the fourteen normal subjects (6 female, median age 32, range 24-49) are also in table 9.

	TGA (n=14)	Controls (n=14)	p value
Age, years	34 \pm 7	32(24-49)	0.64
Age at surgery, median (range), months	10(7-20)	-/-	-/-
Male/female	8/6	8/6	-/-
NYHA functional class I/II	12/2	14/-0	-/-
CMR: Systemic ventricular			
EDVi, mL/m ²	79 \pm 13	70 \pm 15	0.11
ESVi, mL/m ²	35 \pm 4	25 \pm 8	0.002
EF, %	59 \pm 5	66 \pm 5	0.002
Septal ECV	0.254 \pm 0.036	0.23 \pm 0.032	0.03

Table 9: Table comparing controls to those with a systemic RV. EDVi and ESVi refer to indexed ventricular volumes during diastole and systole respectively.

8.3.2 CMR

Mean indexed RV end diastolic volume (RVEDVi) was 79 ± 13 mL/min², mean indexed RV end systolic volume (RVESVi) 35 ± 4 mL/min² and mean RV ejection fraction (RVEF) $59 \pm 5\%$ (Table 9). No patients had any focal, macroscopic areas of LGE. Mean septal ECV in patients was 0.254 ± 0.036 , which was significantly higher than that of normal subjects (0.230 ± 0.032 ; *p* = 0.03). There was no correlation between CMR measures of systemic RV volume or systolic function to septal ECV.

Right Ventricular Free Wall ECV

It was not possible to accurately assess the ECV in the right ventricular free wall (or any other right ventricular segment away from the septum) using the current method. This was mainly due to trabeculation which resulted in myocardial regions of interest partial voluming with blood. The presence of blood in the region of interest will falsely elevate the ECV. The problem is illustrated in Figure 27. This assessment was therefore abandoned and only septal ECV is reported.

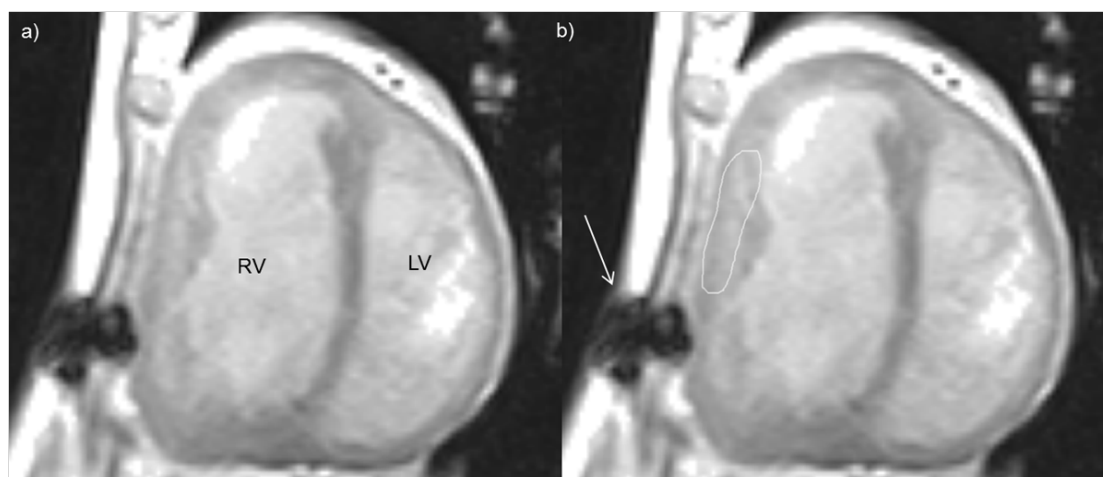


Figure 27: FLASH IR short axis images from a patient with a systemic right ventricle taken at an inversion time of 700ms on contrast infusion is shown. In pane a) the anatomy is depicted (RV = right ventricle and LV = left ventricle). In pane b) the problems in assessing right ventricular free wall T1 are shown. The region of interest drawn partial volumes both blood and myocardium due to trabeculation. Although less important, artefact from sternal wires is also present (arrowed). Partial voluming with myocardium and blood was a problem in nearly all patients in all right ventricular segments.

EQ-CMR and NT-proBNP

Median NT-proBNP was 19.5 (14-45) pmol/L. NT-proBNP showed a positive relationship with septal ECV, $p=0.04$; $r=0.55$ (Figure 28).

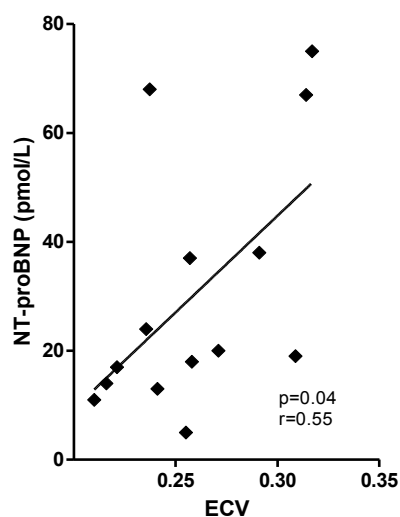


Figure 28: Graph shows positive relationship between increasing NT-proBNP and Septal ECV

EQ-CMR and CPEX testing

CPEX testing provided the following data: mean ChI 0.69 ± 0.21 , mean pVO_2 22 ± 8 ml/kg/min and mean VE/ VCO_2 slope 28 ± 5 (Table 9). There was no association between Septal ECV and either pVO_2

($p=0.24$; $r=0.38$) or VE/VCO_2 slope ($p=0.60$; $r=0.18$). There was; however, a significant negative correlation between septal ECV and chronotropic index ($p=0.04$; $r=0.58$). (Figure 29).

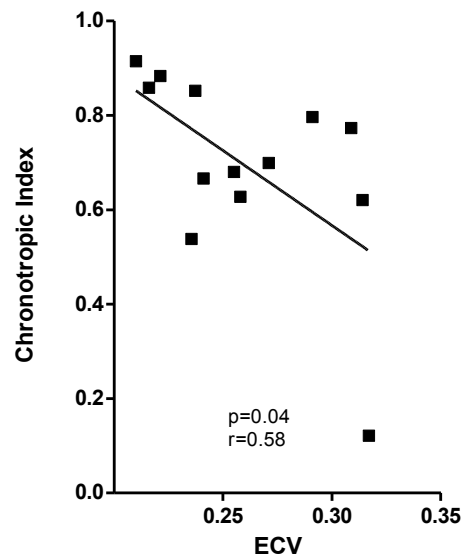


Figure 29: Significant negative relationship between ChI and septal ECV.

8.4 Discussion

This study suggests that diffuse fibrosis is more pronounced in the myocardium of the systemic RV of adults late after palliation of TGA compared to controls. The extent of interstitial expansion was related to known markers of disease severity and outcome parameters (NT-proBNP and ChI) suggesting a potential causative role.

Lifelong maintenance of the systemic circulation by the morphologic RV results in a heart failure phenotype that is associated with significant early morbidity and premature mortality^{4,13}. Evidence is emerging that myocardial fibrosis, determined histologically or by CMR, is a key factor in the development of ventricular dysfunction in patients with both acquired and CHD where pressure overload is the principal insult^{200,201}. Further, LGE on CMR has been linked to prolongation of ECG parameters associated with inhomogeneous electrical activation associated with sudden cardiac death²⁰⁰. Quantifying myocardial fibrosis in patients with systemic RVs also provides an additional measure of disease severity. Further studies are needed to investigate the clinical usefulness of EQ-CMR in predicting outcome in this group.

EQ-CMR has been previously validated as a novel non-invasive technique to quantify diffuse myocardial fibrosis in adults with left ventricular disease²⁰². This current prospective study used a

similar method to identify and quantify diffuse myocardial fibrosis in adults with atrial switch palliation of TGA. The results are similar to those of Broberg *et al*²⁰¹, who used a bolus technique as opposed to EQ-CMR. There are a number of T1 mapping based techniques in development by CMR currently²⁰⁵. The use here of an infusion of gadolinium, to reach contrast equilibrium, eliminates contrast kinetics, which can alter in an individual over time (for example due to changes in body weight or renal function) which may permit more precise evaluation of changes over time in any individual, important both in the clinical and research settings. The technique has been validated against histology in aortic stenosis and hypertrophic cardiomyopathy²⁰². Although the bolus gadolinium technique is perhaps simpler, the total CMR scan time in the cohort remained at around 1 hour for all patients, as the bolus and infusion was given early in the protocol whilst continuing to scan other parameters during equilibration. Despite the differences in study method, the results obtained in both small studies are similar, and suggest that CMR diffuse fibrosis assessment is a useful biomarker in this cohort of patients.

Earlier work has confirmed that focal myocardial scar, as represented by localised late gadolinium enhancement of the myocardium on CMR imaging, can be present in patients with atrial switch palliated TGA, and relates to the systolic function of the systemic RV²⁰⁰. This finding most likely reflects localised surgical insult or coronary insufficiency (due to RV hypertrophy or abnormal coronary circulation). My study did not find that the ECV related to measures of RV size or systolic function. This may reflect the small cohort size involved, or may suggest early pathophysiological detection of disease such that diffuse fibrosis is a precursor to measurable RV dysfunction. It is worth noting that the mean RV ejection fraction of this study cohort was within the perceived normal range. It is possible that such diffuse fibrosis may relate to diastolic dysfunction in the systemic RV; however, this is not straightforward issue in this cohort. Interestingly, diffuse fibrosis was found to relate to NT-proBNP. This is an established neurohormonal marker of disease in the general cardiology population⁹⁶. It is also increasingly being recognised as a valuable tool in CHD, and specifically in TGA, where it correlates to systemic RV function as determined by CMR²⁰⁶. In the general cardiology population NT-proBNP has an established role in detecting asymptomatic left ventricular dysfunction in high-risk populations¹⁴⁰ and in predicting cardiovascular events in those with preserved ventricular function¹⁴¹. The finding of diffuse fibrosis on CMR imaging in the setting of preserved RV systolic function may represent a similar early warning sign.

Septal ECV also showed a negative correlation to ChI, but no relation to pVO₂ or VE/VCO₂ – both established independent markers of outcome in CHD. Giardini and colleagues studied adults with a

systemic RV and previous Mustard or Senning palliation and proposed a VE/VCO₂ slope cut-off >35.4 as being predictive of four-year mortality or cardiac related admission¹⁶² – the majority of patients involved in this study had cut-off values lower than this. Similarly, values for pVO₂ in this cohort were above the levels previously published as predictors of adverse events in congenital cohorts¹⁵⁹. Adults with a systemic RV often describe themselves as well and asymptomatic, despite objective evidence to the contrary. Formal exercise testing has however found that the majority with a systemic RV have chronotropic incompetence and furthermore, that in a proportion of those studied, such inability to increase heart rate was unrelated to metabolic parameters, suggesting that this alone may be causing exercise intolerance¹⁶¹. Whether these findings represents early detection of ensuing RV dysfunction remains to be determined; however, it is likely that any underlying cause is multifactorial. It is of interest to note that a study of adults with hypertrophic cardiomyopathy also found a relationship between delayed Gadolinium enhancement on CMR and blunted heart rate response on exercise²⁰⁷. Such late Gadolinium enhancement has been found to be an independent predictor of deficient exercise capacity in such cohorts²⁰⁸; however, relationship to outcome and underlying mechanism is not yet established.

It is important to note here the small but significant annual incidence of bradyarrhythmias and complete heart block that occur in this population. Such arrhythmias increase with time during follow up¹³, and published frequency of pacemaker insertions vary from 5-11%^{13,209}. It is well recognised that sick sinus syndrome is associated with a diffuse fibrotic process in the sinoatrial node and indeed a recent murine model has recapitulated this²¹⁰. Furthermore, the patients presented in this paper develop increased atrial wall stress and stretch, which will promote local hypertrophy and fibrosis in conjunction with the effects of corrective surgery. Marouche *et al* has recently demonstrated significant correlations between atrial fibrosis using gadolinium enhancement and sinus node disease supporting pathological studies and recent murine models of the process²¹¹. Therefore, although this study did not seek to identify diffuse fibrosis at the sinus node, given the early palliative intervention and subsequent lifelong adverse physiology, it is likely that the septal hypertrophy identified is not an isolated process and similar changes are occurring in the atria and SA node leading to chronotropic incompetence which could be explored as CMR resolution of fibrosis improves.

The septal fibrosis seen on EQ-CMR may therefore underlie the conduction pathway problems that develop in such patients, possibly due to myocardial disarray. It will be interesting to see whether

the degree of abnormality can predict future development of conduction block and the need for pacing.

8.4.1 Limitations

This study is limited in size and further larger scale investigation is needed. Although the results show the potential for the technique to be useful, newer methods for T1 mapping have recently become available and show the potential for higher resolution whole heart mapping in 3 breath holds²¹². These could allow more accurate assessment of the RV free wall, which were not possible to assess in this study.

Despite the presence of RV hypertrophy in the patient cohort, the assessment of diffuse fibrosis in the anterior free wall of the RV was technically problematic. The ubiquitous presence of trabeculation within the systemic RV free wall, leaves very few areas of compacted RV myocardium during diastole that are without blood pool contamination. If zones of blood pool are included in the myocardial analysed region of interest, the ECV would be falsely elevated. Metal artefact from sternal wires also contributed to artefact in this zone in many patients.

8.4.2 Conclusion

There is an increased amount of diffuse fibrosis in the septum of adults with a systemic RV, late after Senning or Mustard palliation for TGA that can be quantified non-invasively. The extent of diffuse fibrosis showed significant association with NT-proBNP measurement and may aid in the identification of patients at risk of developing bradyarrhythmia. Larger and longer-term studies are needed to determine whether such diffuse fibrosis is of prognostic significance and whether its extent can be modified with therapeutic intervention.

My final Chapter sought to take a closer look at the functional status of adults under routine surveillance at my Institution with atrial palliation of TGA. Disease characterisation and relationship to functional ability is not established in this complex cohort and with the information made available from the previous Chapters I wanted to further understand the relationship between objective and subjective assessments of well being.

CHAPTER 9: Quality of life in adults after Mustard or Senning palliation and relationship to other measurements of systemic right ventricular function.

9.1 Introduction

Patients with CHD notoriously underreport their symptoms and physical limitations^{115,191,213}. In clinical practice we often rely on these symptoms to select patients at high risk for adverse events, and hence may neglect a significant group of patients who would benefit from early and targeted therapeutic intervention. Such adverse events are particularly high in substrates where the RV is the systemic ventricle. This is particularly true in the setting of TGA repaired by the Mustard or Senning procedure, with significant morbidity and premature mortality^{4,13}.

In the general population with heart failure several validated self-assessment tools exist, including the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), which provide a numerical estimation of quality of life. These tools measure the impact of disease on many activities of daily living and mental health and are useful to follow progress of disease and efficacy of treatment. None have been tested in the population with a systemic RV however. In this population several objective measures of RV function are emerging, including NT-proBNP²⁰⁶ and certain ECG parameters^{52,105,105}. CMR imaging evaluation of the systemic RV and atrial pathways is an excellent tool in this population, though this investigation can be time consuming, expensive and is not available to all. CPEx testing has recently given rise to an early evidence base for all cause mortality among adults with CHD, including measurements of peak VO_2 and VE/VCO_2 slope^{158,158,159,160}. In adults with a systemic RV and previous Mustard or Senning palliation, a VE/VCO_2 slope cut-off >35.4 has been proposed as being predictive of four-year mortality or cardiac related admission, though this was related to the age at time of exercise and also age at original palliation¹⁶². Both heart rate reserve and ChI have also been found to provide prognostic and predictive outcome data in general cohorts with CHD and in those with a systemic RV^{161,163}.

The inter-relationship between all these measures in adults late after Mustard or Senning palliation is not established. The relationship between these measures and subjective symptom scoring has also not been studied in detail.

9.2 Methods

9.2.1 Study population

This was a prospective study. Data was routinely collected from adults with previous Senning or Mustard surgery for TGA attending a dedicated CHD clinic at The Heart Hospital (London) between January 2010 and July 2011. These adults were included from the same pool of patients as that previously studied. Data included assessment of symptoms by NYHA functional class, measurement of circulating N-terminal pro Brain Natriuretic Peptide (NT-proBNP) levels and renal function, and surface electrocardiogram (ECG). Patients were also invited to fill out a MLWHFQ. CMR imaging and CPEX were performed within 3 months of clinic attendance in accordance with clinic protocols in those also willing to participate in this part of the study. Protocols for ECG, CPEX and CMR have been previously in this Thesis. The study had Institutional approval and all patients gave informed consent to participate in the study.

9.2.2 Quality of Life Questionnaire

Each patient was invited to complete a MLWHFQ¹⁶⁶. This is 6-point (zero to 5) Likert scale, 21 item self-assessment questionnaire that was undertaken at the time of clinic attendance. Scored out of 105, the lower the score, the less the impact of disease. The MLWHFQ contains questions on functional ability, symptoms and mental health, as well as activities of daily living including work, chores and leisure time.

9.2.3 Statistical Analysis

The Kolmogorov-Smirnov test was used to confirm or exclude normal distribution for each variable. Values are expressed as mean \pm standard deviation (SD), median (25-75th percentile values) or percentages, as appropriate. Univariate comparisons were performed by Student's t-test, Mann Whitney U test, and Chi-square test for normally distributed, non-normally distributed and categorical variables respectively. Pearson's or Spearman's correlation coefficients were used as appropriate to look for univariate associations between continuous variables (SPSS Inc., Chicago, USA and GraphPad Software Inc, La Jolla, USA). Differences were considered to be significant at a *P* value of <0.05.

9.3 Results

9.3.1 Patient characteristics

Ninety-two adults were included in the study. No patient died or was admitted with decompensated heart failure between clinic attendance or subsequent CMR or CPEX. Mean age at time of clinic

attendance for the whole cohort was 31±6.5 years. Median age at initial surgical repair was 8 (0.1-96) months. 51% (n=47) underwent Mustard palliation; 60% (n=55) were male. Sixteen (17%) patients had associated ventricular septal defects repaired at original palliation – ‘complex’ anatomy. Seven further patients (8%) underwent later surgical revision of atrial pathways. For the purpose of statistical analysis these 23 patients comprised the ‘complex surgical’ group. The remaining 69 patients had simple TGA and single stage surgery. Table 10 summarises baseline measurements of all investigations.

Twenty-nine patients were taking beta-blockers (32%), 33 angiotensin converting enzyme inhibitors/angiotensin receptor blockers (36%), and 10 were on diuretic therapy (11%). Sixteen (17%) had permanent pacemakers *in-situ* and four (4%) had ICD’s. No patient had CRT *in-situ*.

9.3.2 Quality of Life Assessment

Ninety-two patients completed a MLWHFQ and also had NT-proBNP testing, renal function and resting ECG analysis (Table 10). The median score for MLWHFQ was 6(2-19) for the whole group. MLWHFQ correlated with both age at clinic attendance ($p=0.002$, $r=0.31$) and age at original repair ($p=0.0007$, $r=0.35$).

	All (n=92)	Surgery type		<i>p</i> value	Surgical course		<i>p</i> value
		Mustard (n=47)	Senning (n=45)		Simple (n=69)	Complex (n=23)	
Age, years	31±7	35±8	27±4	<0.0001	31±6	34±8	0.03
Age at surgery, months	8 (0.1-96)	10 (0.1-96)	7 (0.3-48)	0.01	6 (0.3-96)	9(0.1-70)	0.72
Male/female	55/37	31/24	36/16	---	49/27	15/16	---
NYHA functional class I/II	72/19	32/14	40/5	---	65/9	16/13	---
CMR							
RVEDVI, mL/m ²	87±19	89±20	86±18	0.66	83±15	100±25	0.003
RVESVI, mL/m ²	41±15	43±18	40±12	0.54	38±10	52±23	0.005
RVEF, %	56±7	57±8	55±6	0.53	56±7	55±7	0.83
LVEF, %	64±9	64±8	66±6	0.25	64±8	64±12	0.95
NT-proBNP, pmol/L	24 (16-43)	33 (20-72)	19 (11-35)	0.003	23(14-37)	38(23-75)	0.005
ECG (resting)							
QRS, ms	96±20	100±22	88±15	0.008	92±19	110±26	0.0006
QTc, ms	402±27	403±33	394±24	0.09	400±31	412±36	0.14
MLWHFQ	6(2-19)	8(3-28)	4(0-12)	0.03	4(1-13)	14(4-45)	0.004
CPEX							
CI	0.76(0.67-0.84)	0.75(0.56-0.88)	0.77(0.72-0.83)	0.57	0.77(0.69-0.85)	0.73(0.37-0.80)	0.09
Peak VO ₂ , ml/kg/min	24±7	21±6	28±5	0.001	25±6	19±9	0.02
VE/VCO ₂ slope	30±6	31±6	28±6	0.19	30±6	27±3	0.22
ECG (peak exercise)							
QRS, ms	87±15	92±17	81±8	0.01	86±16	98±20	0.03
QTc, ms	406±25	415±27	391±19	0.003	404±32	421±26	0.07
QTd, ms	41±13	41±14	41±13	0.9	40±12	43±17	0.49

Table 10: Showing characteristics of those patients with a systemic RV.

Those with Mustard palliation had a significantly higher score than those with a Senning operation (8(3-28) vs. 4(0-12) $p=0.03$) but this significance was lost when adjusting for age ($p=0.59$). Those with a complex surgical history had a significantly higher score than those with simple surgery (14(4-45) vs. 4(1-13) $p=0.004$) as did those with NYHA II compared to class I (23(7-45) vs. (4(1-12) $p<0.0001$). This finding persisted when accounting for age difference ($p<0.0001$; Figure 30).

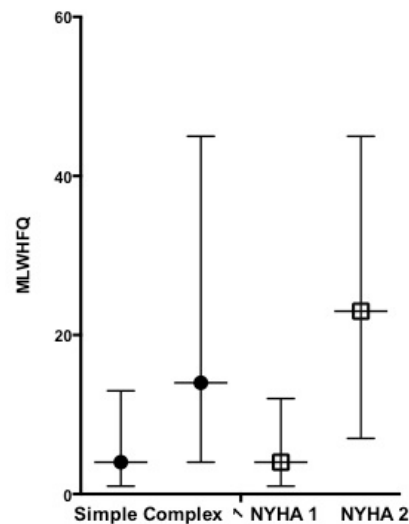


Figure 30: MLWHFQ between those with simple vs complex repair and NYHA class.

For the whole group, median NT-proBNP was 24(16-43) pmol/L, median urea 5.4 (4.5-6.3) mmol/L, mean creatinine 78 ± 17 mmol/L and median sodium 142(141-144) mmol/L. NT-proBNP was significantly correlated to MLWHFQ ($p=0.001$, $r=0.34$) and this relationship nearly maintained significance when correcting for age and age at palliation ($p=0.055$). Urea was also significantly associated with MLWHFQ ($p=0.003$, $r=0.31$) and this relationship persisted when correcting for both age at follow-up and age at palliation ($p=0.021$). Sodium levels revealed a weak relationship to MLWHFQ ($p=0.01$, $r=0.26$); however, this became insignificant when corrected for age ($p=0.51$). Creatinine showed no relationship with MLWHFQ score ($p=0.52$).

MLWHFQ and Electrocardiographic Indices

Mean QRS duration for the whole cohort was 96 ± 20 ms. This parameter showed a significant relationship to MLWHFQ score ($p<0.0001$, $r=0.41$. Figure 31) that persisted following both age corrections ($p=0.002$). QTc interval also revealed a weak correlation to score ($p=0.023$, $r=0.24$);

however, this significance was lost when age-corrected ($p=0.68$). No ECG parameter at peak exercise ($n=54$) showed any relationship with MLWHFQ score.

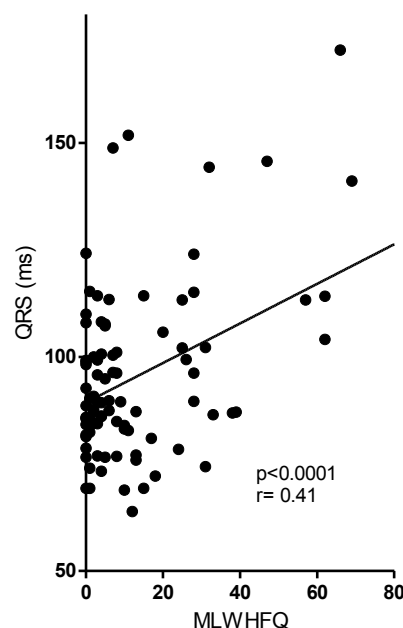


Figure 31: QRS duration is significantly related with MLWHFQ score.

MLWHFQ and CMRI

Fifty-five patients underwent additional CMR imaging. The mean values of the CMR findings for this sub-group are as follows: RVEDVi 87 ± 19 ml/m², RVESVi 41 ± 15 ml/m², RVEF $56 \pm 7\%$ and LVEF $64 \pm 9\%$. Although RVEDVi did weakly relate with MLWHFQ ($p=0.036$, $r=0.29$) this was not the case once the values were corrected for age at follow-up and palliation ($p=0.9$). No other measure related to MLWHFQ in the first instance.

9.3.3 Cardiopulmonary exercise testing

Forty-one patients had full CPEX testing. Median values for ChI were 0.76(0.67-0.84). There was no significant difference between palliative subtypes (Mustard 0.75(0.56-0.88) vs. Senning 0.77(0.72-0.83), $p=0.17$); however, ChI did relate strongly to both age at follow-up ($p=0.0005$, $r=0.45$) and age at palliation ($p=0.0004$, $r=0.46$). Interestingly, ChI did not differ substantially between those with simple or complex surgery (0.77(0.69-0.85) vs. 0.73(0.37-0.80) $p=0.09$); however, when NYHA I was compared to NYHA II there was a significant difference (0.77(0.70-0.85) vs. 0.51(0.26-0.76) $p=0.01$). In keeping with this finding, MLWHFQ did have a relationship with ChI – $p=0.01$, $r=0.34$.

VE/VCO₂ Slope

Mean VE/VCO₂ slope for the whole cohort was 30±6. This parameter showed no significant difference between either palliative subtype or those with complex or simple anatomy (Table 9.1). VE/VCO₂ slope did not relate to age nor age at palliation ($p=0.25$; $p=0.56$). It did however, show a relationship with MLWHFQ ($p=0.0028$, $r=0.48$. Figure 32a).

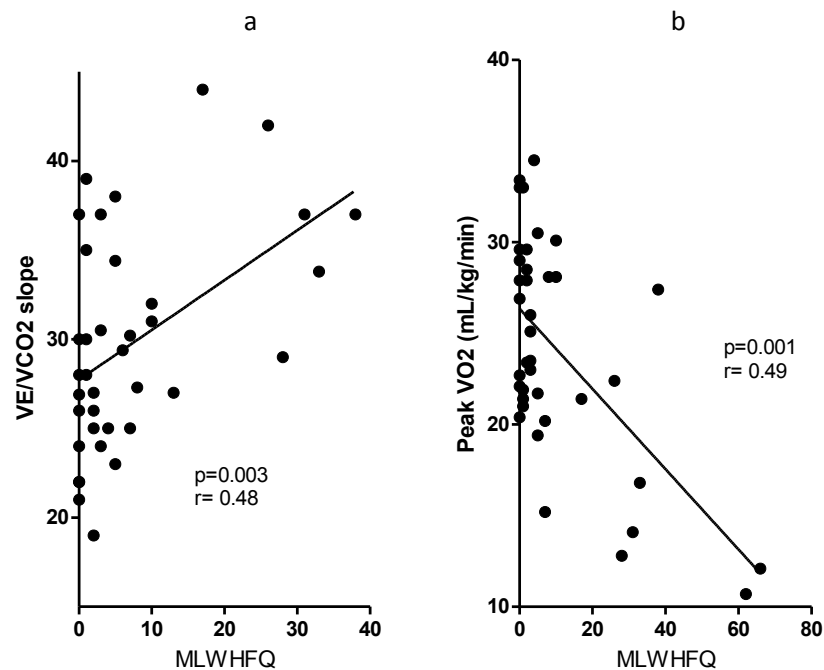


Figure 32: Both VE/VCO₂ slope and peak VO₂ show significant relationships with the MLWHFQ.

Peak VO₂

Peak VO₂ for the cohort was 24±7ml/kg/min. Peak VO₂ was significantly lower in the complex group (19±9 vs. 25±6ml/kg/min, $p=0.02$) and in those with Mustard palliation (21±6 vs. 28±56ml/kg/min, $p=0.001$). Peak VO₂ was also significantly related to age at follow-up ($p<0.0001$, $r=0.60$). Peak VO₂ correlated with MLWHFQ ($p=0.001$, $r=0.49$. Figure 32b) and this relationship persisted once corrected for age and age at palliation ($p=0.003$).

Neither ChI, VE/VCO₂ slope nor Peak VO₂ showed any relationship to CMR measures of RV size or function (Table 11). Neither Peak VO₂ nor VE/VCO₂ slope were related to any ECG parameter at rest or on exercise (Table 11). ChI was however, related to both resting QRS duration ($p=0.0012$, $r=0.41$) and QTc interval ($p=0.01$, $r=0.32$). All parameters showed a relationship with NT-proBNP (Figure 33).

	Chronotropic Index	VE/VCO ₂ slope	Peak VO ₂ (ml/kg/min)
RVEDV(ml/m ²)	p=0.27 r=0.17	p=0.74 r=0.14	p=0.68 r=0.02
RVESV (ml/m ²)	p=0.19 r=0.2	p=0.59 r=0.09	p=0.47 r=0.13
RVEF (%)	p=0.27 r=0.17	p=0.034* r=0.36	p=0.61 r=0.03
LVEF (%)	p=0.89 r=0.02	p=0.55 r=0.11	p=0.27 r=0.17
QRS (ms)	p=0.001* r=0.41	p=0.49 r=0.11	p=0.11 r=0.24
NT-proBNP (pmol/L)	p=0.005* r=0.38	p=0.007* r=0.45	p=0.003* r=0.55

Table 11: NT-proBNP is the only parameter to show significance with each CPEX parameter.

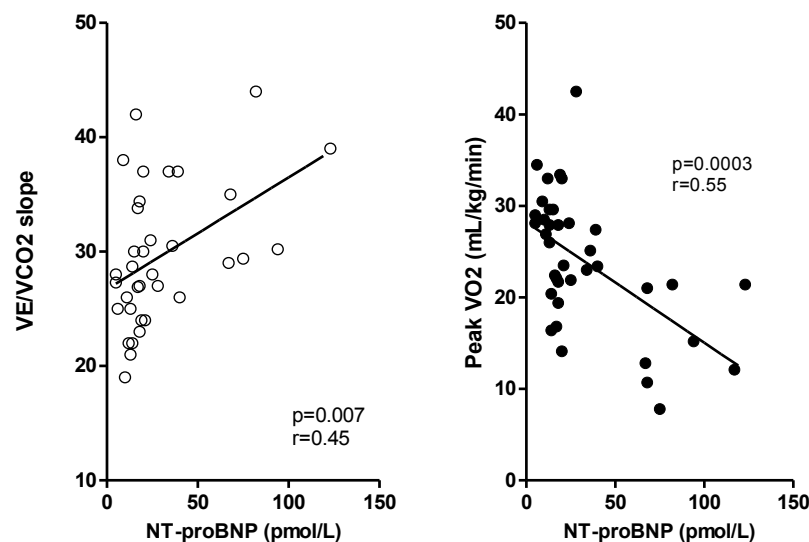


Figure 33: Graphic representation showing significant associations between NT-proBNP and both VE/CVO2 and peak VO2.

Peak exercise electrocardiographic indices

QRS duration, QTd and JTd showed significant shortening at peak exercise compared to at rest (Table 12). No exercise parameter showed a significant relationship with any other parameter, nor was there any relationship when examining the change between the resting and peak exercise figures.

	Resting	Peak	p value
QRS (ms)	97±22	90±18	0.0008
QTc (ms)	403±33	408±31	0.06
QRSd (ms)	31±11	30±9	0.97
QTd (ms)	49±15	41±13	0.002
JTd (ms)	53±15	41±12	0.0004

Table 12: QRS duration, QTd and JTd show significant differences at rest and peak exercise.

Discussion

This is the largest prospective study to date examining subjective self-assessment of status (using MLWHFQ) and comparing it with a variety of measures of disease severity in adults late after Mustard or Senning palliation of TGA.

At present there exists no validated, subjective patient symptom score for those with CHD. Smaller and heterogenous cohorts make any such undertaking complex. Further, and specifically in those with CHD, it is not unusual to see patients who feel and describe themselves as well, despite objective findings to the contrary¹⁹¹. This situation is not aided by the lack of an objective scoring system in this population to help identify those at high risk of adverse events. Such outcomes are particularly prevalent and premature in those with a systemic RV, in particular following atrial redirection surgery for TGA^{4,13}.

This study demonstrated that MLWHFQ score was significantly associated with objective assessment by NYHA functional class over and above the effect mediated by age of the patient at clinic attendance or palliation. This was not the case when considering palliative surgical method, suggesting that this alone does not confer added risk. This is supported by the finding that neither ChI nor VE/VCO₂ slope, both proposed as markers of disease severity and risk in this cohort^{162,162}, are significantly different between the two palliative subtypes.

Subjective symptom score

The MLWHFQ is a simple, practical and readily reproducible self-assessment tool easily applied in the out-patient setting. It is not validated for use in the CHD population, and although the questionnaire encompasses many areas potentially impacted by disease, including leisure, work, health and sexual functioning, it is not designed to measure impact on one dimension over another.

This study found that MLWHFQ scores relate to NT-proBNP levels, but only a clear trend towards significance persisted once values were corrected for age. Cohort size, though large for this

anatomic substrate, may not have been sufficient and larger studies may be necessary. It is interesting to note however, that a study comparing BNP to subjectively assessed health status in a general cohort with heart failure found no correlation between the two factors, despite both showing a correlation to NYHA class²¹⁴. The proposal that subjective measures of impact of disease are not measurable nor reproducible by physiological testing is perhaps supported by another study which determined that raised BNP, in association with depressive symptoms, was associated with a 5.5 times higher risk of cardiac events than when BNP was elevated to the same degree in isolation²¹⁵.

MLWHFQ scores were highly related to QRS duration on the surface ECG. In this cohort, although QRS duration has been associated with increased risk of sudden cardiac death¹⁰⁵, other studies have not described any difference in QRS duration in those who suffered a SCD versus those who did not^{106,106}. Certainly in the general population, QRS duration is an established predictor of all cause mortality^{118,118}¹¹⁹. Interestingly, QRS duration is associated with ventricular size in those with a systemic RV^{36,104}; however, in this study MLWHFQ did not relate to any parameter measured on CMR imaging once the values were corrected for age, suggesting that both the questionnaire and QRS duration are more sensitive determinants of RV pressure overload than the dimensional measurements made by CMR imaging alone. Electromechanical uncoupling, of which QRS duration is a marker, can be mediated by local areas of dyssynchronous activation and subsequent hypertrophy, neither requiring discernable volume overload of the ventricle nor necessitating marked deterioration of global ventricular function in the first instance.

MLWHFQ did show a close association with measured blood urea that was still present after accounting for age of the patient and age at palliation. Neither blood creatinine nor sodium showed a similar relationship. The latter was recently proposed as a strong predictor of mortality in a heterogenous cohort of adults with CHD; however, in my homogenous cohort the sodium levels were higher than in the similar, smaller group with palliated TGA included in this study (142(141-144mmol/L), n=92 vs 137.8±1.8 mmol/L, n=43). Further, even when directly comparing NYHA class I vs. class II in the cohort, no significant difference was found. Further study of this parameter in homogenous cohorts with CHD is thus considered necessary.

It is interesting to note that no CMR parameter of systemic RV size or function correlated in any way with MLWHFQ. This supports the concept that there is no single way to measure HF severity, but rather that this complex disease process requires several different diagnostic and prognostic

measures, including neurohormonal markers, measurement of systemic RV size and function via CMR, symptom scoring, ECG parameters and CPEX testing. CMR imaging may be the gold standard measure of systemic RV function, but it may not be the gold standard measure of HF. In non-congenital cohorts, LVEF is a very poor predictor of survival in acquired HF reflecting the fact that HF becomes a multi-organ disease as it advances.

Cardiopulmonary exercise testing

My study demonstrates that CPEX testing is a valuable additional tool in the characterisation of disease in adults late after Mustard or Senning palliation of TGA. CI, VE/VCO₂ and Peak VO₂ were all related to MLWHFQ, but only the latter maintained significance when correcting for underlying age and palliative age. In patients with repaired ToF, both peak VO₂ and VE/VCO₂ slope were found to be independent predictors for adverse cardiac events¹⁵⁸, and Peak VO₂ recently found to be prognostic in those with Ebstein's anomaly¹⁵⁹. In a cohort of noncyanotic patients, Dimopoulous *et al* found that a peak VO₂ cut-off of <15.5ml/kg/min was associated with a 2.9 fold increased risk of admission or cardiac death compared to those who achieved a Peak VO₂ >15.5ml/kg/min¹⁶⁰. In my cohort, only four patients (9%) achieved under this cut-off and the implications of this can only be known with time.

Dimopoulous and colleagues, in the same cohort, determined that those with a VE/VCO₂ slope >38 had a higher risk of dying within two years (13%) than those who did not (1%)¹⁶⁰. Giardini and colleagues studied adults with a systemic RV and previous Mustard or Senning palliation and proposed a VE/VCO₂ slope cut-off >35.4 as being predictive of four-year mortality or cardiac related admission¹⁶². Seven patients in this current study fulfilled this criterion. Of interest, VE/VCO₂ slope was the only CPEX parameter to relate, albeit weakly, to RVEF as determined by CMR. This suggests that CPEX parameters do not in themselves relate to ventricular size or function directly. In this particular anatomical substrate various other haemodynamic pathophysiologies may exist to affect cardiopulmonary efficacy, most commonly atrial pathway lesions, including baffle obstruction or leak. The inability of the atrial pathways to allow increases in stroke volume sufficiently with exercise as compared to the physiological normal will further compound such efficacy in the absence of visible ventricular dysfunction.

This is the first study to show that VE/VCO₂, ChI and peak VO₂ relate strongly to NT-proBNP in adults late after atrial palliation of TGA, a finding that is consistent in other cohorts with CHD²¹⁶. This suggests that NT-proBNP, as well as being a measure of cardiac ventricular status, is also closely

related to overall functional capacity. Indeed, in the general population with heart failure, BNP measurement both independently and in association with assessment of NYHA functional class has been determined to be indicative of aerobic exercise capacity²¹⁷, and further, BNP levels have been shown to decrease with exercise training in similar cohorts compared to those without exercise training²¹⁸. BNP is a molecular marker of myocardial hypertrophy²¹⁹, whose production is increased under conditions of cardiac stress. Such ventricular hypertrophy, specifically of the RV, is anticipated in this current cohort. BNP may prove to be a valuable marker of early RV disease in this substrate prior to the progression of such hypertrophy to adverse remodeling and objective heart failure and as such guide early investigation and timely therapy. Calculation of RV mass would be necessary to further study this relationship.

Electrocardiography

QRS duration is noted to decrease with exercise²²⁰ and this is the case with my cohort. Physical exercise can provoke malignant arrhythmias in susceptible substrates however this was not seen in this investigation. QTd and JTd are measures of ventricular repolarisation, as QRS duration is a measure of ventricular depolarisation. Reduction of these with exercise, thus reflecting increased homogeneity of ventricular electrical activation, would suggest that risk of malignant arrhythmia be low in this cohort. In a similar group studied with repaired ToF, this was found not to be the case²²¹; however, the change in measured ECG parameters was found to relate to degree of pulmonary regurgitation and RV function and volume. I did not find such a relationship; however, the mechanism of RV insult is different in each substrate thus likely impacting on such a potential relationship.

Conclusion

This is the largest prospective study to date examining the inter-relationship of various measurements in adults late after atrial redirection surgery for TGA. I show that subjective assessment of quality of life with the MLWHFQ is both reliable and practical in the outpatient setting.

DISCUSSION

The number of children surviving with CHD is increasing as a result of improving surgical and catheter techniques available from infancy onwards. With the incidence of all forms of CHD estimated at between 4 to 19 per 1000 live births, there are now equal numbers of adults with CHD as children for the first time. Previously, only those with mild disease tended to survive to adulthood; however, this is clearly no longer the case. Increasingly challenging anatomies and physiologies are being encountered in the surviving adults; however, morbidity and mortality in these relatively young patients are still a major challenge: This burgeoning population brings with it new clinical problems to be identified and addressed following successful palliative and reparative interventions. Increasing age and a desire and ability to have children means that these patients and their physicians face new challenges - These adult patient cohorts still remain relatively uncharacterised compared to their counterparts with structural heart disease.

This Thesis set out with the task of examining the right ventricle in adult CHD. In this challenging, varied and complex patient group, this apparently versatile chamber can serve as both the sub-pulmonary ventricle – it's usual physiologic role – or the systemic ventricle. As such, though morphologically similar, the physiological demands incurred are necessarily very different. Further, even in those anatomies, such as ToF, where the RV serves as the sub-pulmonary chamber, significant short and long-term haemodynamic stresses arise due to abnormal loading conditions relating to both underlying anatomy and previous surgical intervention. This ensures that the electromechanical status of the RV in patients with CHD, whatever the anatomical substrate, is not comparable to those older adults with structural heart disease: Equivalence of therapies, investigative tools and outcome measures in these two cohorts cannot, and must not, be assumed.

This Thesis initially studied adults with a subpulmonary RV, specifically ToF and corrected Pulmonary Stenosis. Both are subject to similar haemodynamic stressors and those with ToF specifically, are bound in a continuous cycle of risk between increasing RV volumes and conduction-repolarisation parameter changes on ECG, a phenomenon that accentuates the close relationship between electrical and mechanical interactions within the myocardium. These ECG changes in turn, are associated with increased risk of malignant arrhythmias and premature demise. Earlier work had already established that PPVI, an alternative to formal surgical pulmonary valve replacement, led to haemodynamic improvements at follow up in this cohort⁴³. This Thesis sought to study the

hypothesis that the amelioration of haemodynamics seen with PPVI was also associated with recovery of ECG parameters. The minimally invasive nature the technique, undertaken without the additional confounding effects of open heart surgery, was thought to enable isolated study of this phenomenon.

I found that electrical remodelling does indeed occur following isolated (pure) pulmonary valve replacement in these patients, and that improvements in measured electrical parameters continues at 1 year of follow-up and that these are accompanied by the expected significant haemodynamic improvements. This suggests that neither haemodynamic nor electrical lesions should be treated in isolation, and that correction of one can infer a positive outcome on the other: Given the minimally-invasive nature of PPVI, and the ever expanding technological advances making such interventions more amenable to other lesions, this is indeed exciting. This project did not unfortunately, include the obvious next stage of study, which would be to determine whether recovery of electrical homogeneity was associated with reduction in arrhythmia risk and therefore, premature sudden cardiac death - further longer term multi-centre studies are necessary to investigate this and this is currently being undertaken.

Following this first study, it became apparent that there is very little information describing the electrical activation pattern of the subpulmonary RV. This is hugely relevant in a cohort of patients at risk of significant morbidity and mortality from progressive HF. I have shown that electrical and haemodynamic integrity are indeed closely related; however, in many with a dysfunctional RV there are no suitable targets for haemodynamic intervention and thus electrical reysnchronisation becomes a feasible alternative therapeutic target.

Mechanical dyssynchrony is intuitively pervasive in all cohorts with CHD, and thus there is a pressing need to consider long term CRT delivery: Despite often considerable technical obstacles related to venous and cardiac anatomy there are already encouraging reports on applying CRT in a variety of CHD patient groups. Specifically in those with RV dysfunction, the literature documents some early successes achieved by extending the concept of CRT to the failing sub-pulmonary ventricle associated with RBBB. My second study thus followed on from the first on the basis that in the same way that correction of haemodynamic compromise can lead to improved electrical homogeneity, resynchronisation of electrical activation can be assumed to allow recovery of haemodynamic function.

In order to appropriately select patients with RV dysfunction for CRT it is first necessary to understand the intrinsic electrical activation pattern through the myocardium in this anatomical substrate. Further, such formal study of the electrical activation pattern of the subpulmonary RV would facilitate targeted lead placement for CRT in this population that would maximise subsequent haemodynamic improvement, and this theory formed the basis for my second project.

My work identified the intrinsic electrical activation pattern present on the surface of the RV in adults with similar haemodynamic lesions as those included in my first study. This cohort however, underwent open (surgical) correction of their haemodynamic lesion but represented a relatively low risk group for inclusion in the study. I was able to generate an epicardial map, which confirmed that previous surgical insult, in the form and location of transannular patch repair, was associated with greatest delay in electrical activation. Identification of those areas of the RV surface subject to greatest delay in activation allowed me to guide best placement of epicardial wires for subsequent resynchronisation pacing. I found that single site RV pacing targeted to the region of latest intrinsic activation induced acute improvements in central haemodynamics, supporting the concept of subpulmonary “RV CRT” in this cohort. Targeted pacing to the latest area of activation in such patients has therapeutic potential both in the acute post-operative and chronic setting, and is superior to RV apical pacing which may be detrimental. This latter is particularly relevant since long-term bradycardia pacing often has the RV lead positioned at the RV apex.

Future work would involve generation of an endocardial electrical map, perhaps using an endocardial array possibly at the time of EP study or pacemaker insertion, with long-term follow-up of targeted pacing: It would be interesting to see if the acute haemodynamic improvements seen in my preliminary study translate into long-term reverse remodelling of the RV. Further, imaging modalities and parameters which identify dyssynchrony and predict a positive response to pacing need to be identified and their relationship to the surface ECG established. These tools would ideally help identify patients for resynchronisation therapy in the same way that currently exists in the general cardiac population. Lastly, after delivering CRT we must judge success using clinically meaningful endpoints.

From a starting point of understanding the impact of electrical inhomogeneity, as measured by surface ECG parameters, on the long term outcome in those with a subpulmonary RV, my Thesis set out to study two different methods of ameliorating this risk. I identified the electrical activation sequence and examined the process of electrical resynchronisation and remodelling and its

relationship to mechanical dyssynchrony and resolution of haemodynamic compromise. In those with a systemic (subaortic) RV, however; very little is known even regarding ECG parameters that might represent future risk in terms of malignant arrhythmia and SCD. For the next section of my Thesis therefore, I elected to undertake a comparison of ECG's of those adults with a systemic RV who remained under follow up with those who had died, in an attempt to identify similar predictive and easily applied ECG parameters.

I determined that certain ECG parameters are indeed related to increased risk of death in this high risk group of adults – both QRS duration and QTc interval are independently related to mortality. Interestingly, the cut-off values I found are within the perceived 'normal' range for the general adult population, therefore necessitating consideration of the highly abnormal physiological stresses placed on the morphological right ventricle in the subaortic position. I propose that serial monitoring of the surface ECG for these parameters should form a routine assessment in all patients with atrial redirection surgery for TGA. In association with a clinical suspicion of arrhythmia, a QRS duration >104ms and/or QTc interval >406ms should prompt full investigation and consideration, as necessary, of early initiation of anti- heart failure and/or anti arrhythmic therapies.

Having studied potential ECG parameters to identify risk in those adults with a systemic RV, I was keen to study the relationship of these parameters with the function of that chamber, and further, examine other markers that might enable risk stratification and lead to targeted intervention that could, in the long term, positively affect outcome in this group of patients. I therefore included measurement of the novel biomarker NT-proBNP with study of the relationship between specific surface ECG measurements to the function of the systemic RV. NT-proBNP, measured by a simple, routinely available blood test, has recently come into its own in the general cardiac population as a rule-out determinant of cardiac stress, and I was interested to see whether it also had a role in those with systemic RV. I showed a close relationship existed between NT-proBNP, ECG parameters and measures of systemic RV function as determined by CMR- considered the gold standard tool for assessment of the systemic RV. Both 12 lead ECG and NT-proBNP measurements are widely available in the outpatient setting, and constitute safe and cost effective surrogate markers of systemic RV function, thus providing useful information easily and quickly on heart failure status. This is particularly important since these patients tend to underreport their functional status and these tools provide a simple objective assessment. My findings dictate that this same cohort should be studied sequentially to fully determine the association of these parameters with long-term outcome – in the same way that ECG cut-offs are found within the perceived normal range, it is likely

that cut-offs for NT-proBNP will be different from those currently used in the general cardiology population.

This research therefore supports the role of NT-proBNP as a viable blood biomarker in adults with a systemic RV. Having evaluating plasma biomarkers, I subsequently elected to examine diffuse fibrosis on CMR, to evaluate its potential as an imaging biomarker of disease. Diffuse fibrosis has previously been described in those with primary left ventricular disease, and I felt its presence in the systemic RV might provide further information about this complex disease process. The majority of adults with CHD will undergo CMR imaging at least once in their lifetimes, and likely many will undergo this serially. Diffuse fibrosis in the systemic RV was found to be significantly associated with NT-proBNP levels, further supporting its role as an imaging biomarker. An unexpected additional finding was the relation of diffuse fibrosis to chronotropic index, suggesting that this disease processes is not limited to the ventricular myocardium since this heart rate variation is mediated by the sino-atrial node. Diffuse fibrosis is likely to aid identification of patients at risk of developing significant bradyarrhythmia, and it would be interesting if further studies could extrapolate future risk in this regard. Larger and longer-term studies are therefore needed to determine whether such diffuse fibrosis is of prognostic significance and, importantly, whether its extent can be modified with therapeutic intervention.

To complete this Thesis I chose to assess objective and subjective measures of disease characteristics in those adults with a systemic RV. These patients, like their peers at all levels of CHD, tend to underreport their symptoms: This can lead to overestimation of clinical status and the unfortunate possibility of clinically significant problems presenting late. This Thesis has already provided evidence for the role and application of several early warning parameters and I was keen to see how these related to subjective functional status as measured with the MLWHF questionnaire. This latter is not validated for use in the adult congenital heart population despite being routinely employed.

My findings confirmed that this well-validated tool for assessing symptoms and quality of life in patients with HF relates strongly to NT-proBNP levels, ECG parameters and exercise capacity in adults with a systemic RV. The ability of the MLWHFQ, or similar quality of life assessment, to identify adults with CHD at risk of HF related events needs further evaluation – at present this research shows that it constitutes an important screening tool which can be easily applied in the regular outpatient clinic. Future work would see this tool employed on regular visits and the trend

over time examined and related to the other parameters presented in this Thesis. With time, it might be possible to propose a new scoring system targeted for HF in adults with CHD by using aspects of both the current NYHA classification and MLWHFQ.

In conclusion, this Thesis has provided the foundation for future work on two fronts- improved identification of early heart failure in CHD using simple plasma and imaging biomarkers, and the potential role of RV resynchronisation. This former needs to be expanded to international prospective longitudinal studies to further validate this Thesis' conclusions and identify other early markers of decline in systemic RV function in order to facilitate earlier device or pharmacological intervention. The pacing study illustrates how early intervention with resynchronisation has the potential to reverse, or at least stabilise, systemic RV function in these patients: Strategies utilizing discrete targeted leadless electrodes are emerging and these offer significant opportunities to precisely target pacing and even personalize resynchronization in these complex substrates.

PUBLICATIONS ARISING DURING THIS THESIS

Original Papers

Plymen CM, Sado DM, Bolger AP, Lambiase PD, Taylor AM, Hughes M, Moon JC. "Diffuse Myocardial Fibrosis in the systemic right ventricle of patients late after Mustard or Senning surgery. An Equilibrium Contrast Cardiovascular Magnetic Resonance Study". Accepted in *Eur H J Cardiovascular Imaging*. 2013

Plymen CM, Bolger AP, Lurz P, Nordmeyer J, Lee TY, Kabir A, Coats L, Walker F, Deanfield JE, Taylor AM, Bonhoeffer P, Lambiase PD. "Electrical remodelling following percutaneous pulmonary valve implantation – Author's Reply." *Am J Cardiol* 2011 **107**: 1867-68

Plymen CM, Bolger AP, Lurz P, Nordmeyer J, Lee TY, Kabir A, Coats L, Walker F, Deanfield JE, Taylor AM, Bonhoeffer P, Lambiase PD. "Electrical remodelling following percutaneous pulmonary valve implantation" *Am J Cardiol* 2011 **107(2)**: 309-14

Plymen CM, Hughes ML, Picaut N, Panoulas VF, MacDonald ST, Cullen S, Deanfield JE, Walker F, Taylor AM, Lambiase PD, Bolger AP. "The relationship of systemic right ventricular function to ECG parameters and NT-proBNP levels in adults with transposition of the great arteries late after atrial switch repair". *Heart* 2010 **96**: 1569-57

Case Reports

Butcher CT, Plymen CM, Walker F. "Chest pain, breathlessness and ST elevation in a 21 week pregnant woman - A diagnostic and management challenge". *BMJ Case Reports*, 2010; bcr0320102853 - bcr0320102853.

Butcher CT, Plymen CM, Walker F. A novel and unique treatment of right ventricular inflow obstruction in a patient with a Bjork modification of the Fontan palliation before pregnancy. *Cardiol Young* 2010 **20**: 337-338

Submitted for peer review

Plymen CM, Finlay M, Tsang V, O'Leary J, Picaut N, Cullen S, Walker F, Deanfield JE, Hsia TY, Bolger AP, Lambiase PD. Haemodynamic consequences of targeted single and dual site right ventricular pacing in adults with congenital heart disease undergoing surgical pulmonary valve replacement. To: *Circ EP*

Abstracts

Plymen CM, Finlay M, Tsang V, Picaut N, Cullen S, Walker F, Deanfield JE, Hsia TY, Bolger AP, Lambiase PD. Targeted Single And Dual Site Right Ventricular Pacing In Adults With Congenital Heart Disease Undergoing Surgical Pulmonary Valve Replacement. **Heart Rhythm Society**, Boston, May 2012.

Plymen CM, Sado DM, Bolger AP, Lambiase PD, Taylor AM, Hughes M, Moon JC. Diffuse myocardial fibrosis in adults late after palliation of transposition of the great arteries and relation to parameters of heart failure severity. **ESC Heart Failure**, Belgrade, May 2012

Plymen CM, Lambiase PD, Hughes ML, Picaut N, Panoulas VF, Cullen S, Deanfield JE, Walker F, Taylor AM, Bolger AP. A validated score for the assessment of heart failure severity in adults late after Mustard or Senning palliation of transposition of the great arteries. **ESC Heart Failure**, Belgrade, May 2012

Sado DM, Plymen CM, Bolger AP, Lambiase PD, Taylor AM, Hughes M, Moon JC. Equilibrium contrast CMR in the systemic right ventricle of adults late after Mustard or Senning surgery for transposition. **Society of Cardiovascular Magnetic Resonance**, Orlando, February 2012

Plymen CM, Finlay M, Tsang V, Picaut N, Cullen S, Walker F, Deanfield JE, Hsia TY, Bolger AP, Lambiase PD. Haemodynamic consequences of targeted single and dual site right ventricular pacing in adults with congenital heart disease undergoing surgical pulmonary valve replacement. **Heart Rhythm Congress**, Birmingham, October 2011

Plymen CM, Panoulas VF, Picaut N, Cullen S, Walker F, Deanfield JE, Bolger AP, Lambiase PD. QRS and QTc intervals on 12 lead ECG predict survival in adults late after atrial switch palliation of transposition of the great arteries. **European Society of Cardiology**, Paris, August 2011.

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Plymen CM, Lambiase PD, Bolger AP, Lee TY, Nordmeyer J, Lurz P, Coats L, Taylor AM, Deanfield JE, Bonhoeffer P. Electrical remodelling following percutaneous pulmonary valve implantation. **Heart Rhythm Society**, Boston, and **British Cardiac Society**, London. *Heart* 2009; **95**: 35

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APPENDICES

A. Percutaneous Pulmonary Valve Implantation

Percutaneous pulmonary valve implantation (PPVI) was performed at three centres (The Heart Hospital, Harley Street Clinic, Great Ormond Street Hospital - London) by operators trained in the procedure. All patients had congenital heart disease and right ventricular outflow tract dysfunction.

PPVI was undertaken in all patients under general anaesthesia. Aseptic techniques were observed in all. Haemodynamic monitoring was performed invasively and all procedures were carried out under fluoroscopic guidance. This enabled assessment of the right ventricular outflow tract and quantification of pulmonary regurgitation prior to commencement and determined final suitability for the procedure.

The percutaneous pulmonary valve is a bovine jugular vein valve mounted (sutured) within a platinum-iridium stent (NuMed, Hopkinton; Medtronic Inc, Minneapolis, USA (Figure 34). The valves are preserved within a solution of glutaraldehyde and alcohol and were therefore washed thoroughly with saline prior to implantation.



Figure 34: The percutaneous bovine jugular venous valve mounted within an expandable platinum-iridium stent (NuMed, Hopkinton, USA)

The valved stent was crimped down over the barrel of a sterile 2ml syringe and then front-loaded on to the delivery system (NuMED, Hopkinton, USA). Further crimping of the stent was performed to mould it around the 'balloon in balloon' delivery system and it was then carefully retracted within the polytetrafluoroethylene sheath covering.

The femoral vein was dilated to 22 French and under X-ray guidance the front loading delivery system was advanced directly into position over an ultra stiff exchange guide wire, which was secured in a distal pulmonary artery. The sheath was retracted from the valved stent and partial deployment was achieved by inflation of the inner balloon. Following final angiographic confirmation of the valve position, the outer balloon was inflated to complete deployment. Anatomy dictated balloon size, varying between 18mm, 20mm and 22mm.

Repeat angiography and pressure measurements were made to confirm a positive outcome. Intravenous broad-spectrum antibiotics and heparin were administered at the time of the procedure. On site surgical cover was available during each procedure in case of emergency.

B. Surgical Pulmonary Valve Replacement

Surgical (open) pulmonary valve replacement was undertaken by two trained operators (VT; TYH) at one centre (The Heart Hospital, London) in adults with significant pulmonary regurgitation and RV dilatation. All patients had undergone previous childhood repair of ToF or congenital pulmonary stenosis. Each patient signed written consent for inclusion in this study. The surgical procedure has been described previously, but is as follows²²¹:

Following the induction of general anaesthesia with invasive pressure monitoring and the placement of external defibrillator, redo sternotomy was undertaken with an oscillating saw and the lower table of the sternum was opened with Mayo scissors. Adhesions were divided with diathermy. All cases were performed under routine cardiopulmonary bypass on the beating heart with ascending aortic and bicaval cannulation at 28–32°C. In case of residual ventricular septal defect or other intra-cardiac lesion requiring attention, aortic cross clamping with cold blood cardioplegia was used.

The native main pulmonary artery was dissected out and circumferentially transected close to the ventriculo-arterial junction. The branch pulmonary arteries were sized, and dealt with if necessary. A longitudinal incision was made into the proximal outflow tract. Any hypertrophied muscular trabeculations in the subjunctional region would be divided to create a widely open pathway. In patients with aneurysmal RVOT patch, the akinetic thin area was excised leaving a small fibrous rim at the muscular margin, followed by plication with 4–0 Prolene to reconstruct the outflow tract. This infundibuloplasty aims to improve the distorted right ventricular outflow tract geometry and reduce the cavity size. The homograft was tailored in length to connect with the distal pulmonary artery

using 5–0 Prolene. The proximal end of the homograft valve was inserted within the newly created muscular ‘sleeve’ for functional support (Figure 35). Trans-oesophageal echocardiography was used to assess valve patency and function.

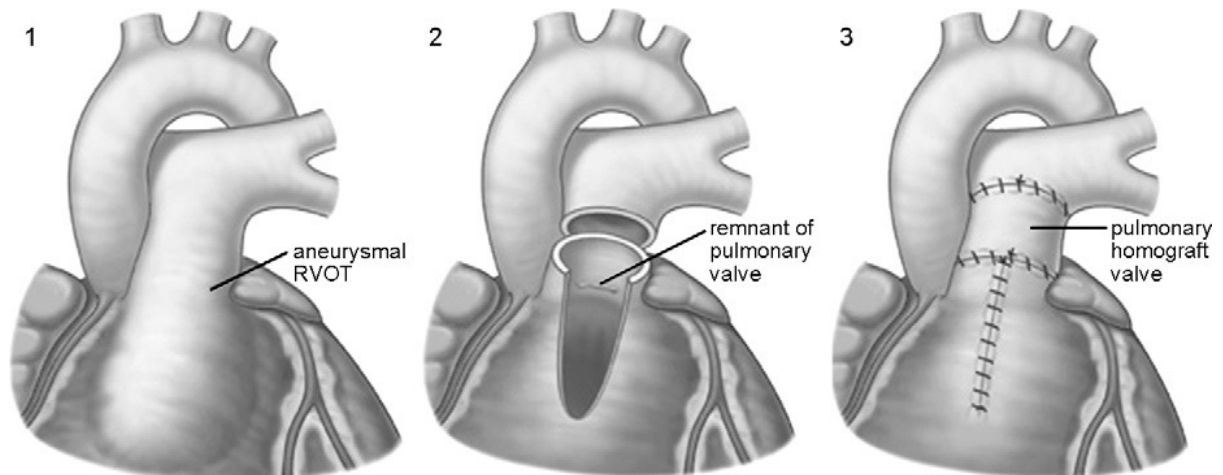


Figure 35: Diagrammatic representation of the surgical technique for pulmonary valve replacement Coats *et al*, *Eur J Car Thor Surg* 2005 **27**: 536-43 Copyright © 2005, European Association for Cardio-Thoracic Surgery, with permission.